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Paranimfen	Drs. K.J. Langenhuijsen Drs. C.S. Aarts

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Introduction
Introductie

Chapter 1 Introduction

1.1 General introduction

Prostate cancer is the most common cancer in Dutch men with an incidence in 2009 of 102 in 100.000 men [1]. This means an estimated 9600 new cases are diagnosed each year. With the ageing population the number of newly diagnosed patients is expected to rise to an estimated 15,000 in 2015. It is currently the second leading cause of cancer death after lung carcinoma. The lifetime chance of prostate cancer in Dutch men is the largest of all cancers with almost 10% [2].

Although 70% of these men is older than 65 years, and prostate cancer is mainly a disease of the elderly, a shift is seen towards younger age. Several factors have contributed to this increase of prostate cancer diagnosis over the last decades. The most important has been the introduction of serum PSA measurements into medical practice, which has led to dramatic changes in the incidence of prostate cancer, i.e., increased detection rates and a stage reduction at the time of diagnosis. Another significant factor was the expanding use of transrectal ultrasound-guided needle biopsies. The PSA threshold for biopsies has declined with time due to the detection of significant cancers in low PSA ranges [3]. The trend towards earlier detection was accompanied by a lower mean age at diagnosis, and subsequently an increased number of curative treatments were applied with an improved 5-year relative survival [4]. In spite of the high prevalence of this disease, the chance of dying of it is much smaller. Autopsy studies have shown that approximately 60% of men in their sixth and seventh decade of life have prostate cancer and generally do not die of it [5]. This means significant over detection of prostate cancer that can lead to excessive curative treatments and treatment-related complications.

Classically, the curative treatment options for localized prostate cancer are radical prostatectomy and radiotherapy (external beam radiotherapy (EBRT) and brachytherapy). Significant side effects have been described for both surgery and radiotherapy, and include urinary incontinence, erectile dysfunction and radiation related toxicity to the surrounding tissues, i.e., bladder, anal canal and rectal mucosa. Rectal toxicity is one of the limiting factors and is directly related

to the total radiation dose prescribed and the volume of the rectal wall receiving a high dose [6]. On the long run radiotherapy related malignancies are described as well. The concept of dose escalation in EBRT has gained popularity amongst radiation oncologists as the clinical outcome has improved with lower PSA recurrence rates [7]. The prostate is a moving target, which necessitates wider treatment margins around the prostate for adequate irradiation of the tumor [8]. As a consequence, the total radiation dose to surrounding healthy tissues is one of the limiting factors. New developments in radiotherapy techniques are focusing on measures to deliver high-dose radiation to the prostate with smaller margins around the organ. Treatment techniques have improved and intensity-modulated radiation therapy (IMRT) modulates radiation dose to the organ more accurately than three-dimensional conformal radiotherapy (3D-CRT). A second means of reducing complication rates is by precisely targeting the organ with image-guided radiotherapy and fiducial intraprostatic gold markers. These markers are used for daily position verification and correction of the prostate gland and the clinical benefits are being investigated at this moment. Recently, the implantation of gold markers in the prostate bed for salvage radiotherapy after radical prostatectomy was introduced as well [9], but complication rates of this procedure have not been described before. Further, little is known about the side effects of the intraprostatic marker implantation and therefore these were investigated by us. Another means of influencing irradiation to surrounding tissues is by reduction of the organ volume and tumor size with the use of neoadjuvant hormonal therapy. Volume reduction leads to better local tumor control and perhaps to less treatment-related side effects of surrounding tissues [10]. The duration of hormonal pre-treatment is a matter of discussion. It is influenced both by the synergistic effect between hormonal therapy and radiotherapy on one hand, and by the potential of maximal prostate volume reduction on the other hand.

The percentage of men in the Netherlands undergoing radical prostatectomy almost doubled to 20% between 2004 and 2006. Active surveillance was chosen less often from 38% in 1989 to 9% in 2006 [4]. Radical prostatectomy, both open, laparoscopically, and robot assisted comes with a substantial number of side effects and therefore a range of alternative treatment strategies for localized disease, i.e., high intensity focused ultrasound (HIFU) and cryosurgery were

developed. In the early 60s, prostate cryosurgery using liquid nitrogen resulted in severe and frequent complications such as incontinence, and rectourethral fistulas [11]. Therefore, cryosurgery was abandoned until the late 1980s. More accurate TRUS-guided transperineal placement of ultrathin cryoprobes and gas-based cryosurgery [12], with real-time monitoring of the freezing process and a urethral-warming catheter has significantly decreased the number of complications.

So far, the curative treatment options for a local recurrence after radiotherapy were limited to salvage surgery and complication rates, especially incontinence, were more prominent (45%) than with primary radical prostatectomy [13]. Third-generation cryosurgery can potentially be an alternative treatment option and is currently being explored worldwide for its use in this setting. Further, an increasing interest in focal therapy with the use of cryosurgery has been developed.

Hormonal therapy is mainly administered in metastatic disease for long periods of time. Prostate cancer is expected to become castrate resistant after an average of 2 years. The early side effects of this chemical castration are substantial, and consist of hot flushes, fatigue, loss of libido, and erectile dysfunction. On the long run osteoporosis, anemia, loss of muscle mass, metabolic syndrome, and an increased cardiovascular risk are seen [14,15]. In an attempt to improve these complication rates, hormonal therapy can be administered in an intermittent schedule. Pre-clinical studies have shown an improved time to progression and a delay of the castrate resistant state [16,17], but human studies have not confirmed these findings. Other potential advantages of intermittent therapy are the improvement of quality of life during the off-treatment intervals and the prevention of long-term side effects. The patient selection seems critical, but little is known so far about which patients would benefit most of such a treatment regimen.

In this thesis the aforementioned developments in prostate cancer treatment and the complication rates are analyzed and discussed.

1.2 Outline of the thesis

There is a growing concern about the complication rates of curative prostate cancer treatment. A shift is seen towards earlier diagnosed disease, potentially leading to treatment of indolent prostate cancers. Hormonal therapy for metastatic prostate cancer is often administered for several years and the long term complication rates seem substantial. In this thesis, several clinical studies of prostate cancer treatment are described, which aim at improvement of complication rates without compromising the oncological results.

During a course of EBRT the prostate moves in different directions and is therefore called a 'moving target'. It is critical to visualize the organ on a day-to-day basis for adequate targeting of the prostate and to correct for these movements. This can be done with the aid of fiducial intraprostatic gold markers that are visible on electronic portal images. In **chapter 2** the effects of gold marker-based prostate position verification and correction on planning target volume and on radiation doses to surrounding healthy tissues are described. The gold markers are implanted in the prostate without anesthesia, either transrectally or perineally by transrectal ultrasound guidance. As marker implantation is an important tool for prostate localization during EBRT nowadays, the acceptance among radiotherapists and urologists is high. The patient, however, will only accept this procedure if complication rates are low. For a large cohort of patients the complication rate and risk factors for complications, after transrectal implantation of gold markers, were analyzed and are described in **chapter 3**. The role of gold markers is expanding and only recently its use in radiotherapy for a local recurrence after radical prostatectomy has been introduced. In **chapter 4** the technique and complications of transrectal implantation of gold markers in the prostate bed are analyzed. Urologists are increasingly searching for alternative treatment options for localized disease, with potentially less side effects than surgery or EBRT. For local recurrences after EBRT only salvage surgery remains a treatment option. Cryosurgery was developed as an alternative minimally invasive curative treatment option for localized disease and for local recurrences of prostate cancer after EBRT. In **chapter 5** an outline is given of the scientific evidence for the use of third-generation cryosurgery by a systematic review of the

literature. In **chapter 6** an introduction is given for the role of neoadjuvant and intermittent hormonal therapy. The optimal duration of androgen deprivation for maximal prostate volume reduction, in a cohort of patients scheduled for EBRT, is described in **chapter 7**. Finally, an analysis was performed to identify subgroups of patients with metastatic prostate cancer that could benefit from intermittent hormonal therapy. The goals of the study, described in **chapter 8**, were to analyze the predictive value of PSA for progression and the role of testosterone kinetics on quality of life in patients with metastatic disease during continuous or intermittent hormonal therapy.

Hoofdstuk 1 Introductie

1.3 Algemene introductie

Prostaatkanker is de meest voorkomende kanker bij Nederlandse mannen met een incidentie van 102 per 100.000 mannen in 2009 [1]. Dit komt neer op een geschat aantal nieuwe gevallen van 9600 per jaar. Het aantal nieuwe patiënten met prostaatkanker zal waarschijnlijk stijgen tot rond de 15.000 in 2015 door de vergrijzing van de bevolking. Na longkanker is het momenteel de tweede oorzaak van overlijden aan kanker. De kans op prostaatkanker bij Nederlandse mannen gedurende het leven is bijna 10% en daarmee de hoogste van alle kankers [2].

Prostaatkanker is voornamelijk een ziekte van oudere mannen en 70% is boven de 65 jaar, maar er wordt een verandering gezien van presentatie naar jongere leeftijd. De toename van de diagnose prostaatkanker in de laatste decennia komt door een aantal factoren. De belangrijkste is de introductie van de serum PSA-meting in de dagelijkse praktijk geweest, met als gevolg een enorme verandering in incidentie van prostaatkanker met niet alleen een toename van detectie als gevolg maar ook een verschuiving naar lagere stadia tijdens de diagnose. Een andere factor is het toegenomen gebruik van transrectale echografie met biopten. Met de tijd is de ondergrens van PSA voor het nemen van biopten gezakt, omdat ook bij lagere PSA waarden significante prostaatkanker werd gevonden [3]. Door deze trend naar vroege detectie is de leeftijd van patiënten bij de diagnose verlaagd met als gevolg daarvan het inzetten van meer curatieve behandelingen en een verbetering van de relatieve 5-jaars overleving [4]. Ondanks de hoge prevalentie van de ziekte is de kans om eraan te overlijden veel kleiner. Uit obductiestudies is gebleken dat ongeveer 60% van de mannen in de leeftijd van 60 tot 80 jaar prostaatkanker heeft maar hieraan over het algemeen niet overlijdt [5]. Dit betekent dat er sprake is van significante overdetectie van prostaatkanker die kan leiden tot overmatige curatieve therapie met een toename van behandelingsgerelateerde complicaties.

Van oudsher zijn de curatieve behandelingsopties voor gelokaliseerd prostaatcarcinoom de radicale prostatectomie en radiotherapie (uitwendige radiotherapie en brachytherapie). Bij chirurgie en radiotherapie worden significante bijwerkingen door de behandeling beschreven, waaronder urine-incontinentie, erectiele disfunctie en bestralingsgerelateerde effecten op de omgevende weefsels zoals de blaas, het anale kanaal en het rectum. Rectum toxiciteit is een beperkende factor en is direct gerelateerd aan de totale bestralingsdosis en het rectumvolume dat een hoge dosis krijgt [6]. Er worden ook secundaire maligniteiten gezien ten gevolge van de radiotherapie op de lange termijn. Het concept van dosis-escalatie bij uitwendige radiotherapie heeft aan populariteit gewonnen bij oncologische radiotherapeuten door de betere klinische resultaten met lagere PSA recidief kansen [7]. De prostaat is echter een bewegend orgaan en daardoor zijn ruimere behandelingsmarges rondom de prostaat nodig om adequate bestraling van de tumor te bewerkstelligen [8]. Als gevolg daarvan is de totale bestralingsdosis van de omgevende gezonde weefsels een belangrijke beperkende factor. Bij de nieuwe ontwikkelingen in de radiotherapie ligt de nadruk op technieken die afgifte van hoge bestralingsdosis op de prostaat met kleine marges eromheen mogelijk maken. De behandelingstechnieken zijn verbeterd en met de komst van intensiteitgemoduleerde radiotherapie (IMRT) wordt de bestralingsdosis beter verdeeld over het orgaan dan bij 3-dimensionale conformele radiotherapie (3D-CRT). Een andere manier om de bijwerkingen te verminderen is door exacte lokalisering van de prostaat met beeldgeleide radiotherapie en goudmarkers. Deze markers worden gebruikt voor het dagelijks verifiëren en corrigeren van de positie van de prostaat en de klinische voordelen worden momenteel onderzocht. Zeer recent werd ook de implantatie van goudmarkers in de prostaatloge na een radicale prostatectomie geïntroduceerd ten behoeve van ‘salvage’ bestraling [9], maar de complicaties hiervan werden nog niet eerder beschreven. Verder is er weinig bekend over de complicaties van implantatie van goudmarkers in de prostaat en dit werd daarom door ons onderzocht. Een andere manier om bestraling van omgevende weefels te verminderen is door het orgaanvolume en de tumorafmetingen te reduceren met behulp van hormonale voorbehandeling. De volumereductie geeft een betere lokale tumorcontrole en mogelijk minder behandelingsgerelateerde bijwerkingen van de omgevende weefsels [10]. Er is een discussie gaande over de duur van hormonale voorbehandeling. De optimale duur

wordt bepaald door het synergistische effect van de combinatie van hormonale therapie en radiotherapie aan de ene kant en het maximale volumereducerende-effect aan de andere kant.

Het percentage mannen in Nederland dat een radicale prostatectomie onderging tussen 2004 en 2006 is bijna verdubbeld tot 20%. De keuze voor 'active surveillance' daalde van 38% in 1989 naar 9% in 2006 [4]. De radicale prostatectomie, zowel open als laparoscopisch en robot-geassisteerd, geeft een significant aantal bijwerkingen en dit heeft geleid tot de ontwikkeling van een aantal alternatieve behandelmethoden voor gelokaliseerde ziekte zoals hoge-intensiteit gefocusseerde echografie (HIFU) en cryochirurgie. In de vroege jaren 60 werd cryochirurgie van de prostaat verricht met vloeibare stikstof en dit leidde vaak tot ernstige complicaties zoals incontinentie en rectourethrale fistels [11]. Cryochirurgie werd daarom tijdelijk verlaten tot de late jaren 80. Met de introductie van gasgebaseerde cryochirurgie, die exacte plaatsing van zeer dunne cryonaalden mogelijk maakte door middel van transrectale echografie, een urethra verwarmingskatheter *in situ* en het 'real-time' monitoren van het vriesproces [12], is het aantal complicaties significant afgenomen.

Tot zeer recent waren de opties voor behandeling van een lokaal recidief na radiotherapie beperkt tot 'salvage' chirurgie met nog meer complicaties tot gevolg, zoals incontinentie bij 45% van de patiënten, dan bij primaire radicale prostatectomie [13]. De toepassing van een potentiële alternatieve therapie voor deze indicatie, de derde-generatie cryochirurgie, wordt momenteel wereldwijd geëxploreerd. Verder is er een toenemende interesse gaande in focale therapie met gebruik van cryochirurgie.

Hormonale therapie wordt voornamelijk toegepast bij gemetastaseerde ziekte gedurende langere perioden. Na gemiddeld 2 jaar worden tumoren echter castratieresistent. Er zijn aanzienlijke bijwerkingen bekend op korte termijn van chemische castratie zoals opvliegers, vermoeidheid, libidoverlies en erectiestoornissen. Op langere termijn worden osteoporose, anemie, spiermassaverlies, metaboolsyndroom en een verhoogd cardiovasculair risico gezien [14,15]. Met behulp van intermitterende therapie wordt getracht deze

bijwerkingen te verminderen. In preklinische studies werd een langere tijd tot progressie en een vertraging van castratieresistentie aangetoond [16,17], maar dit werd niet bevestigd in studies bij de mens. Een verbetering van kwaliteit van leven tijdens de tussenliggende periodes zonder hormonen en preventie van bijwerkingen op langere termijn zijn andere potentiële voordelen. Patiëntenselectie lijkt hierbij essentieel, maar tot op heden is weinig bekend over welke patiënten de meeste baat hebben bij deze manier van behandelen.

In dit proefschrift worden de hiervoor genoemde ontwikkelingen in de behandeling van prostaatkanker en de complicaties ervan geanalyseerd en bediscussieerd.

1.4 Overzicht van het proefschrift

In toenemende mate komt er aandacht voor de complicaties van curatieve behandelingen bij prostaatkanker. Er is een trend naar vroege diagnostiek van de ziekte met als gevolg een potentiële toename van behandeling van indolente prostaatkanker. Bij gemetastaseerde ziekte wordt vaak meerdere jaren hormonale therapie gegeven met aanzienlijke bijwerkingen op de lange termijn. In dit proefschrift worden enkele klinische studies naar behandeling van prostaatkanker beschreven die als oogmerk een afname van complicaties hebben zonder de oncologische resultaten te verminderen.

De prostaat beweegt in verschillende richtingen tijdens een radiotherapie behandeling en wordt daarom wel een 'moving target' genoemd. Het is essentieel om dit orgaan dagelijks tijdens de behandeling in beeld te brengen voor een adequate instelling van de bestraling en voor correctie van de bewegingen van de prostaat. Dit is met behulp van goudmarkers in de prostaat, die zichtbaar zijn op elektronische 'portal images', te bewerkstelligen. In **hoofdstuk 2** worden de effecten beschreven van de op goudmarkers gebaseerde verificatie en correctie van de prostaatpositie op het geplande doelvolume en op de bestralingsdosis die het omliggende gezonde weefsel krijgt toegediend. Deze goudmarkers worden zonder anesthesie transrectaal of perineaal ingebracht in de prostaat met behulp van transrectale echografie. Dit is tegenwoordig een geaccepteerde procedure

onder radiotherapeuten en urologen omdat de goudmarkers een belangrijke hulp zijn voor lokalisatie van de prostaat tijdens de radiotherapie. Voor de patiënt is de procedure echter alleen acceptabel als het aantal complicaties laag is. Het aantal complicaties en de risicofactoren voor complicaties werden geanalyseerd in een groot cohort van patiënten, na transrectale implantatie van goudmarkers en beschreven in **hoofdstuk 3**. De rol van goudmarkers is recent uitgebreid met het gebruik ervan bij radiotherapie van een lokaal recidief na radicale prostatectomie. In **hoofdstuk 4** worden de techniek en complicaties van transrectale implantatie van goudmarkers in de prostaatloge geanalyseerd. Urologen zijn steeds op zoek naar alternatieve behandelingen voor gelokaliseerde ziekte met potentieel minder bijwerkingen dan chirurgie of uitwendige radiotherapie. Bij het lokale recidief na uitwendige radiotherapie blijft alleen nog 'salvage' chirurgie een behandelmogelijkheid. Cryochirurgie werd ontwikkeld als alternatieve en minimaal invasieve curatieve behandeling voor gelokaliseerde ziekte en voor lokale recidieven van prostaatcarcinoom na uitwendige radiotherapie. In **hoofdstuk 5** wordt door middel van een systematische review van de literatuur een uiteenzetting gegeven van het wetenschappelijk bewijs voor het gebruik van derde-generatie cryochirurgie. **Hoofdstuk 6** bevat een introductie voor de rol van hormonale voorbehandeling en intermitterende hormonale therapie. In een cohort patiënten die uitwendige radiotherapie ondergingen wordt in **hoofdstuk 7** de optimale duur van hormonale behandeling voor een maximale volume-afname van de prostaat beschreven. Tot slot werd een analyse verricht ter identificatie van subgroepen van patiënten met gemetastaseerd prostaatcarcinoom die baat zouden kunnen hebben bij intermitterende hormonale therapie. De doelstellingen van de studie in **hoofdstuk 8** waren het analyseren van de voorspellende waarde van PSA voor progressie en de rol van de testosteronkinetiek voor kwaliteit van leven bij patiënten met gemetastaseerde ziekte tijdens hun continue of intermitterende hormonale therapie.

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Chapter

02

Reduction of radiotherapy margins with intraprostatic gold markers

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Peter van Kollenburg • Johannes H.A.M. Kaanders • J. Alfred Witjes • Emile N.J.Th. van Lin

Chapter 2

Reduction of treatment volume and radiation doses to surrounding tissues with intraprostatic gold markers in prostate cancer radiotherapy

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Abstract

Background: High-precision radiotherapy with gold marker implantation is a standard technique for prostate cancer treatment. To provide insight into the beneficial effect of gold markers, the influence on treatment volume and radiation doses to healthy tissues was investigated.

Patients and Methods: Three consecutive treatment margins were constructed, for 10 patients with localized prostate cancer, to show the reduction of planning target volume: PTV 10 mm (no markers), PTV 7 mm (markers), and PTV 7/5 mm (markers and online correction). On planning computed tomography (CT) scan, the prostate, bladder, rectal wall, and anal canal were contoured. The treatment volume and radiation doses to surrounding organs were calculated. In 65 patients, with the online protocol and gold markers, late toxicity was evaluated.

Results: With gold markers a significant PTV reduction of 27% was achieved ($P < 0.001$). Subsequently, radiation dose reductions to the mean of 17% (±4.5%) to the bladder, 19% (±4.7%) to the anal canal, and 12% (±3%) to the rectal wall, respectively were seen ($P < 0.001$). With 5-mm posterior margins an additional PTV reduction of 3.7% ($P < 0.001$) and total radiation dose reduction to the mean of 24% (±4%), and 16% (±4.5%) to anal canal and rectal wall, respectively were seen ($P < 0.001$). Late grade 1–2 genitourinary and gastrointestinal toxicity was seen in 32%, and 33%, respectively. Grade 3 toxicity was less than 10%.

Conclusions: This study showed a significant reduction of treatment volume and radiation doses to healthy tissues with intraprostatic gold markers.

Introduction

Clinical trials have shown a dose-response relationship in external beam radiotherapy (EBRT) for prostate cancer [1-4]. Dose escalation with higher radiation doses to the surrounding tissues, e.g., bladder, rectum, and anal canal, however, increases toxicity rates [5]. Also, prostate motion is an important source of treatment error, with day-to-day gland displacements of 3–5 mm [6]. 3D treatment margins around the gland are defined to account for these prostate movements and to deliver an adequate dose to the gland. This so called planning target volume (PTV) inevitably leads to higher radiation doses to the surrounding organs. Therefore, strategies to control the patient set-up variations and organ motion have been developed in order to enable minimizing these margins. Among other modalities of image-guided radiotherapy (e.g., cone-beam computed tomography [CT]), an important strategy is to implant gold markers as fiducials for the prostate position and for daily alignment of the gland before radiation is administered. Gold markers have an excellent visibility on electronic portal images that are made during radiotherapy, enabling precise prostate localization and thereby the use of smaller treatment margins. Therefore, intraprostatic gold marker implantation for prostate localization and correction is now becoming the standard in EBRT [7]. Besides implantation by radiation-oncologists with prostate brachytherapy experience, gold markers are often implanted by urologists and 2 groups have described their technique of marker implantation [8,9]. There are few data quantifying the degree of spared healthy tissue with image-guided radiotherapy even in radiation oncology literature. Recently, a dosimetry planning study was reported about the impact of smaller margins and sparing of healthy tissues [10]. The objective of this study is to comprehensively describe the advantages of gold markers for high-precision radiotherapy, especially for urologists who are involved in gold marker implantation, and to report toxicity rates of patients who were treated according to the latest radiation technique.

Therefore, the influence of gold marker-based prostate position correction on treatment volume and radiation doses to surrounding tissues was measured.

Patients and Methods

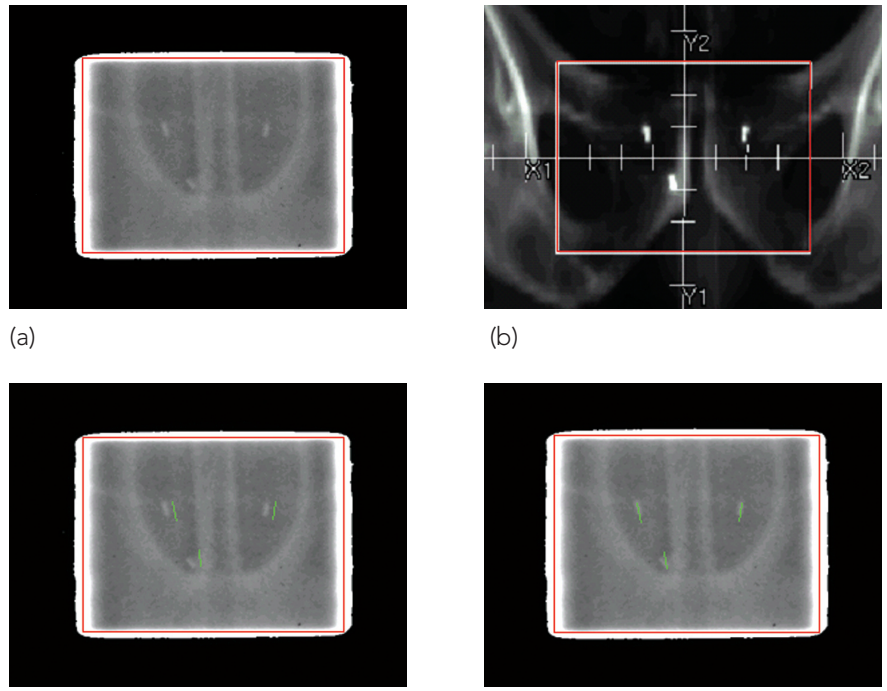
Planning target volume margins

In the past decennium, EBRT, prostate imaging, and patient positioning and verification techniques have gradually evolved in our radiation oncology department. Three time frames can be distinguished, in which different correction strategies were applied, each strategy allowing for specific treatment margins.

Until 2002, no markers were implanted. The daily positioning, during 3D-conformation radiotherapy (3D-CRT), was based on skin marks and reference laser lines. In addition, an offline correction strategy was used in which portal images were obtained during the first treatment fractions. The bony structures of the pelvis on these portal images were compared with a reference image, obtained during the radiotherapy preparation, to estimate the systematic position error. Using an offline correction strategy, large systematic errors in patient position were then corrected for in the subsequent fractions. However, the day-to-day patient set-up variation and the interfraction prostate movement could inherently not be corrected for, because the prostate itself was not visible and the bony structures only served as a surrogate for the gland. Consequently, the margins around the prostate were chosen relatively wide, i.e., 10 mm in all directions.

In 2002, intraprostatic gold marker implantation was introduced in our hospital. The excellent visibility of these markers on the portal images enabled verification of the actual prostate position and subsequently correction of possible positioning errors (Figure 1). The improvement in patient positioning obtained in this way allowed for a margin reduction to 7 mm in all directions. However, day-to-day prostate variations, e.g., under influence of variable bladder and rectum filling, were still uncorrected for.

From 2004, online correction protocols were used, characterized by position verification and correction prior to each treatment fraction. Initially, only an online protocol in the anteroposterior direction was applied to limit the workload on the treatment machines. As published previously, the online correction strategy resulted in a reduction in position variation, which allowed a margin reduction



(a) (b)

(c) (d)

Figure 1

Position verification and correction of the prostate with gold markers: (a) Portal image of anteroposterior (AP) radiotherapy treatment beam, with 3 intraprostatic gold markers. (b) AP reconstruction of a planning computed tomography (CT) scan image for reference of portal image (c) Daily position verification and correction of gold markers. In white, the intraprostatic gold marker position on that specific treatment day. In green, the gold marker position as intended for that treatment day. Image taken before matching. (d) After correction, executed with a fully automated treatment table, the gold marker position matches with the intended marker position.

to 5 mm posterior [11]. In the other directions, no online correction was applied and consequently, the margins remained 7 mm. Recently, a remotely-controllable treatment couch became available, and the online correction protocol can now be executed in all directions without increasing the workload. In addition to smaller treatment margins, intensity-modulated radiotherapy (IMRT) has gradually

replaced 3D-CRT for improved normal tissue sparing. Since 2005, all prostate patients have been irradiated with an endorectal balloon for anorectal sparing [12]. Although the previously-mentioned reductions in treatment margins seem small, the effect on treatment volume is large, as is demonstrated by the following, hypothetical, example. When the prostate is seen as a sphere with a diameter of 4 cm, and 3D treatment margins of 10 mm are applied, the treated volume equals 4/3 x π x radius3 = 4/3 x π x 33 = 113 cm^3. When these margins are reduced to 5 mm, the same calculation leads to a treated volume of only 65 cm^3. In this study, the effect of these reductions on anorectal and bladder doses is investigated.

Patients

In 10 consecutive patients with localized prostate cancer (T1-3N0M0), 3 IMRT plans were constructed per patient. All patients were referred to the radiation oncology department for EBRT with curative intent and have actually been treated according to the latest online correction protocol with IMRT. Prior to treatment planning, each patient received 3 cylindrical intraprostatic gold markers transrectally, 1.2 mm in diameter and 5 mm in length (QLRAD, Zwolle, The Netherlands), in an outpatient setting.

Treatment planning

From each patient, a planning CT scan of the pelvic region (AcQSim big-bore spiral CT scanner; Philips Medical Systems) with 3 mm slice thickness was obtained in a supine position. The patients were asked to empty the bladder and rectum and drink half a liter of fluid, 1 hour before the CT scan. On the CT scan slices the prostate, bladder, rectal wall, and anal canal were contoured using the Pinnacle3 radiation treatment planning system (Philips Medical Systems).

After defining the treatment volume, the 3 investigated PTVs were constructed, simulating the previously-mentioned situations: PTV 10 mm (no markers), PTV 7 mm (markers), and PTV 7/5 mm (markers and online correction), respectively (Figure 2). The treatment was planned with a 5-field IMRT arrangement with a prescribed dose of 78 Gy in 2-Gy daily fractions using 10-megavolt photon beams. The radiation doses, applied to the surrounding organs, were calculated by this treatment planning system.

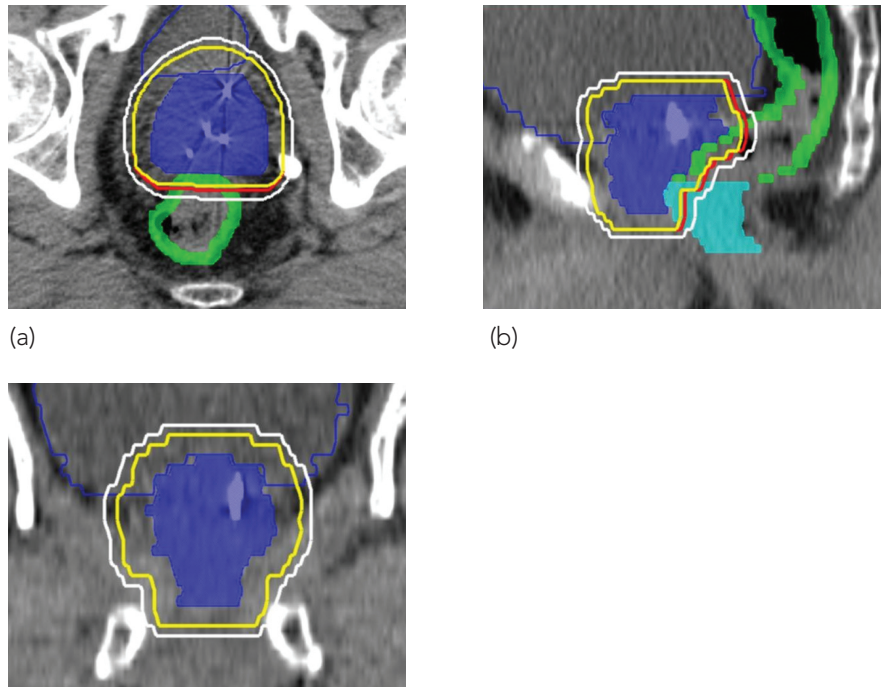


Figure 2

Planning target volume (PTV) constructions: (a) Transverse plane of computed tomography (CT) scan image. PTV 10 mm (white line), PTV 7 mm (red line) and PTV 7/5 mm (yellow line) are outlined. Gold markers are visible. (b) Reconstruction of sagittal plane with different PTVs outlined. (c) Reconstruction of coronal plane.

Organs outlined: bladder (blue line), rectum (green line). Prostate and anal canal are entirely filled out (blue, light blue).

Dose volume histogram analysis

For each treatment plan, dose volume histograms (DVH) were generated for the organs at risk, to visualize the relative organ volume (y-axis) exposed to a radiation dose (Gy) equal to or higher than the value on the x-axis.

Toxicity

From 2008, a consecutive group of 93 patients irradiated in our hospital, with 3D-CRT or IMRT, using an online correction protocol with gold markers and an endorectal balloon, prospectively filled out the Expanded Prostate Cancer Index Composite (EPIC) questionnaires. The acute genitourinary (GU) and gastrointestinal (GI) toxicity rates were scored within 3 months with the modified Radiation Therapy Oncology Group (RTOG) system [13]. For a subgroup of patients, with minimum of 3 years follow-up, the late toxicity rates could be evaluated.

Statistical analysis

The statistical analysis was performed with SPSS 16.0 for Windows (SPSS Inc., 1989-2005). Paired samples t tests were used to calculate the volume differences between the 3 investigated PTVs. Furthermore, the corresponding relative reductions in radiation doses to the bladder, anal canal, and rectal wall were calculated by the same tests. Differences with $P < 0.05$ were considered statistically significant.

Results

Planning target volumes

In all treatment plans, the PTV was adequately covered by the prescribed radiation dose. The mean prostate volume was 43 ml with a subsequent mean PTV 10 mm of 157 ml. For the PTV 7 mm and PTV 7/5 mm treatment plans, the mean irradiated volumes were 115 ml and 111 ml, respectively (Table 1). This corresponded to a significant mean PTV reduction of 27% as a result of using gold markers ($P < 0.001$). A further PTV reduction of 3.7% ($P < 0.001$) was achieved with 5 mm posterior margins. The largest PTV reduction occurred in a small prostate (35%), and the smallest reduction in a large prostate (25%).

Normal tissues

The mean radiation doses to the bladder, anal canal, and rectal wall are outlined in Table 2. The PTV 7 mm plans showed a significant reduction to the mean of radiation doses to surrounding tissues. A reduction of 17% ± 4.5% (standard deviation) to the bladder, 19% (±4.7%) to the anal canal, and 12% (±3.1%) to

Table 1

Planning Target Volume (PTV) for different treatment margins in prostate cancer radiotherapy.

Patient Number	Prostate Volume (ml)	PTV 10 mm (ml)	PTV 7 mm (ml)	PTV 7/5 mm (ml)
1	41	166	120	115
2	49	172	128	123
3	110	310	240	233
4	40	159	115	111
5	33	135	96	93
6	59	194	146	141
7	18	96	65	63
8	22	114	79	74
9	36	140	101	97
10	18	87	60	57
Mean Volume	43	157	115	111
Standard Deviation	27	64	52	51

the rectal wall, respectively, was achieved ($P < 0.001$). The PTV 7/5 mm plans did not significantly influence the mean bladder dose. The mean doses to the anal canal and rectal wall, however, showed a 24% (±4%) and 16% (±4.5%) reduction, respectively, as compared with the PTV 10 mm plan ($P < 0.001$).

In Figure 3, the mean DVHs of all treatment plans are shown. The consequences of margin reductions for the exposure of the surrounding tissues to high dose radiation are illustrated. When the percentage of rectum and anal canal receiving 70 Gy is considered, i.e., the dose that predicts for bowel toxicity [10], a clear reduction is seen with gold markers and an even further reduction with 5 mm posterior margins.

Table 2

Mean radiation doses to surrounding tissues of the prostate in different treatment plans.

Mean Radiation Dose	PTV 10 mm	PTV 7 mm	PTV 7/5 mm
Bladder (Gy)	25 (± 10.9)	21 (± 9.6)	21 (± 9.7)
Anal canal (Gy)	35 (± 11.0)	28 (± 10.1)	26 (± 9.2)
Rectal wall (Gy)	29 (± 4.6)	25 (± 4.3)	24 (± 4.4)

Data are presented as mean (± SD). Abbreviation: PTV = planning target volume.

Table 3

Toxicity rates for online radiation therapy protocol with gold markers, 3D-CRT, IMRT, and endorectal balloon.

Toxicity Grade	Gastrointestinal		Genitourinary	
A. Acute Toxicity				
0	67	(73)	62	(67)
1	21	(23)	16	(17)
2	4	(4)	11	(12)
3		0	4	(4)
B. Late Toxicity				
0	41	(64)	38	(59)
1	19	(30)	4	(6)
2	2	(3)	17	(26)
3	2	(3)	6	(9)

Data are presented as n (%). Abbreviations: CRT = conformation radiotherapy; IMRT = intensity-modulated radiotherapy.

Toxicity

Acute Grade 1–2 GI and GU toxicity was seen in 27%, and 29%, respectively (Table 3). Acute Grade 3 toxicity was rare and no Grade 4 toxicity occurred. In 57% of these patients radiation treatment was performed with 3D-CRT. Late Grade 1–2 GI and GU toxicity was found in 33%, and 32%, respectively after mainly 3D-CRT (94%). Late Grade 3 toxicity was less than 10%.

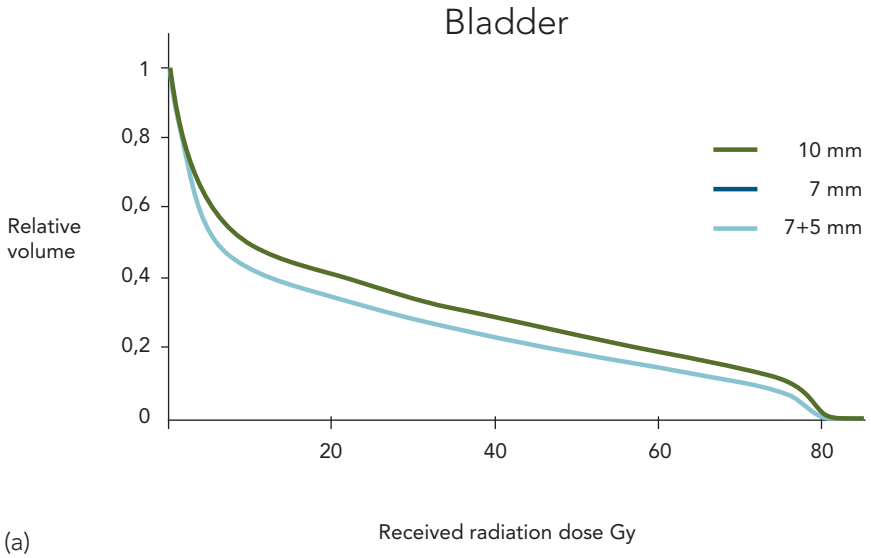
Discussion

In our clinic every patient referred for EBRT receives intraprostatic gold markers. This study was performed to demonstrate the positive effect of gold marker- based margin reductions on radiation doses that are applied to surrounding healthy tissues. In 10 consecutive patients a margin reduction of 3 mm circumferentially, because of the use of gold markers, led to a mean PTV reduction of 27%. The PTV reduction was more prominent in small prostates. The mean doses to the surrounding tissues, i.e., the bladder, anal canal, and rectal wall, have decreased significantly with 17%, 19%, and 12%, respectively. After the introduction of a 5-mm posterior margin, in the online protocol, a further reduction of radiation doses to the anorectal tissues was achieved.

Systematic set-up errors and interfraction prostate motion form important sources of treatment errors [14]. With gold markers, for daily localization of the prostate, the margins around the gland can be reduced. Several feasibility studies have shown the reliability of fiducial markers for prostate position verification during radiotherapy [15,16]. The marker position in the prostate is stable and migration or dislocation of markers is rare [17-19]. The interuser variability of marker detection is low and in our experience the transrectal implantation technique is easy and the complication rates of implantation are low [20]. Besides the transrectal implantation, the transperineal implantation under local anesthetic was also shown to be feasible and safe without negatively influencing the patients' quality of life [21]. Two reports that were recently published have shown the feasibility of marker placement in an outpatient setting [8,9], which we have performed in all patients as well.

Figure 3

Mean dose volume histograms (DVH) of 3 different treatment plans: On the y-axis the relative organ volume exposed to a dose (Gy) equal to or higher than the value on the x-axis for (a) the bladder, (b) the rectal wall (Rwall), and (c) the anal canal (Acanal).



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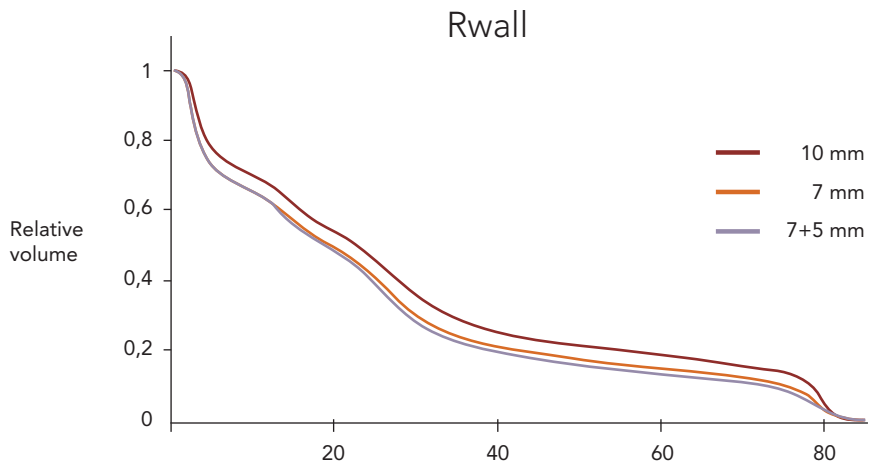

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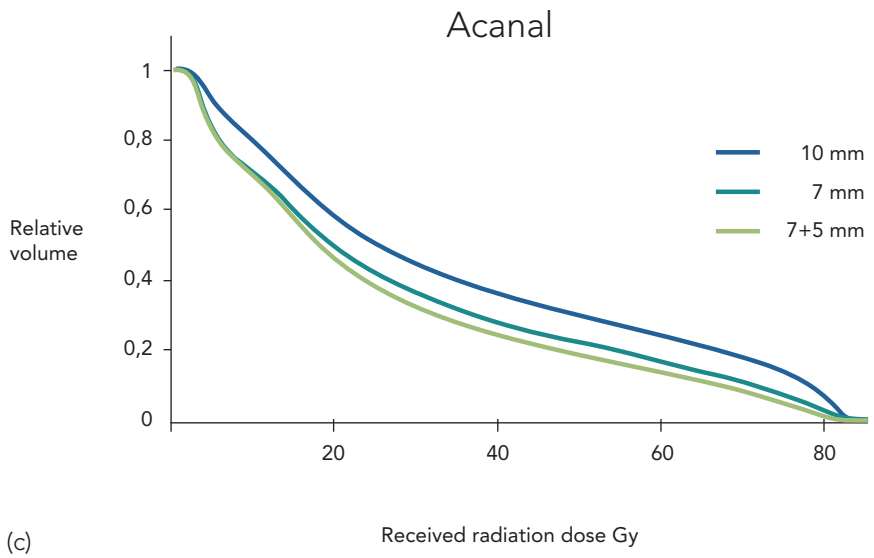

(c)

Several studies report on a dose-effect relation for anorectal toxicity (i.e., a higher dose to these organs leads to higher toxicity rates) [22,23]. Our results have shown that smaller margins with intraprostatic gold markers led to reduced irradiation of healthy surrounding tissues. This will probably result in lower toxicity. Others have indicated that dose coverage to the prostate with intraprostatic markers and image-guided radiotherapy is adequate, in spite of these smaller margins [24].

In our series, the acute toxicity rates compare favorably with a series published by Chung et al. [24]. They found acute Grade 1–2 GI and GU toxicity rates of image-guided IMRT with gold markers, and 2–3 mm circumferential margins of 60%, and 100%, respectively. No acute Grade 3 toxicity was seen. On the contrary, Zelefsky et al. [25] reported acute Grade 1–2 GI and GU toxicity rates of 26%, and 66%, respectively, in 772 patients undergoing high-dose IMRT without markers. No acute Grade 3 GI toxicity occurred, and Grade 3 GU toxicity in only 1 patient. Our 3-year follow-up shows a relatively high rate of late Grade ≥ 2 GU toxicity, compared with other series, in which 15% was shown for IMRT [26]. In spite of this, most complaints were mild and consisted of micturition frequency more than twice the pretreatment frequency. One explanation could be the use of 3D-CRT instead to IMRT. Zelefsky et al. compared conventional 3D-CRT and IMRT, and found dose-dependent acute symptoms, which were precursors of late toxicity, and further a reduced risk for GI toxicity with IMRT. In spite of the use of 3D-CRT, late Grade ≥ 2 GI toxicity rate was low in our series. The 5-mm posterior margins and the endorectal balloon might have contributed significantly to reduced late rectal toxicity, which was shown before in a comparative study of 3D-CRT with endorectal balloon [12]. Given the previously-mentioned dose-effect relations for anorectal and bladder toxicity, application of smaller margins, as is discussed in the present study, might lead to a reduction in these toxicity rates. Comparing the toxicity profiles between different studies is difficult, because the radiation techniques, doses, and treatment margins are different.

The long-term clinical benefits of intraprostatic gold markers for the correction of prostate position during EBRT have not been investigated extensively. Although it seems reasonable to presume that gold markers have a favorable impact on late toxicity profiles, this needs further investigation. As the clinical advantages

of gold marker implantation for localization purposes are so obvious, prospective randomized studies will probably never be performed. At least, a precise long-term follow-up should be pursued to get a clear view of the late toxicity advantages.

Conclusions

Because of the excellent visibility of gold markers, the prostate localization and position correction is more accurate. As a result, the margins around the prostate involving healthy tissues can be reduced. In this study, a margin reduction of 3 mm circumferentially, because of gold markers, leads to a mean treatment volume reduction of 27%. This results in a significant decrease of radiation doses to surrounding healthy tissues. A further reduction is seen with an online correction protocol with 5-mm posterior margins. As dose-escalation protocols will increase toxicity rates, the use of intraprostatic gold markers for margin reduction has become important. The effect on late toxicity profiles needs further investigation.

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Chapter

03

Gold markers for prostate radiotherapy: complication rate and risk factors

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Lisette P. van der Vight • Gill M. McColl • Andries G. Visser • J. Alfred Witjes

Chapter 3
Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors

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Int J Radiat Oncol Biol Phys 2007; 69: 671-76.

Abstract

Purpose: To report the complication rate and risk factors of transrectally implanted gold markers, used for prostate position verification and correction procedures.
Methods and Materials: In 209 consecutive men with localized prostate cancer, four gold markers (1 × 7 mm) were inserted under ultrasound guidance in an outpatient setting, and the toxicity was analyzed. All patients received a questionnaire regarding complications after marker implantation. The complications and risk factors were further evaluated by reviewing the medical charts.
Results: Of the 209 men, 13 (6.2%) had a moderate complication, consisting of pain and fever that resolved after treatment with oral medication. In 1.9% of the men, minor voiding complaints were observed. Other minor transient complications, defined as hematuria lasting > 3 days, hematospermia, and rectal bleeding, occurred in 3.8%, 18.5%, and 9.1% of the patients, respectively. These complications were seen more often in patients with advanced tumor stage, younger age, and shorter duration of hormonal therapy.
Conclusion: Transrectal gold marker implantation for high-precision prostate radiotherapy is a safe and well tolerated procedure.

Introduction

Dose escalation in external beam radiotherapy (RT) for localized prostate cancer improves the outcome, with a lower prostate-specific antigen recurrence rate [1, 2]. Rectal toxicity is one of the limiting factors and is directly related to the total radiation dose prescribed and the volume of the rectal wall receiving a high dose [3]. Prostate motion is considered a source of treatment error, with day-to-day gland displacements of 3–5 mm [4]. To account for these prostate movements, treatment margins of ≤ 10–15 mm must be defined around the gland, resulting in additional irradiation of the surrounding tissues. To enable margin reduction, radiopaque markers implanted in the prostate have been used as an aid for exact localization of the prostate during RT [5-8]. Electronic portal imaging systems are widely used for daily prostate position verification and correction procedures [9-12]. The markers are implanted before acquisition of the planning computed tomography (CT) scan. Gold markers are easily visible fiducials on pretreatment imaging (CT, magnetic resonance imaging [MRI]) studies and megavolt portal imaging during RT sessions. Marker migration within the prostate during the course of RT has been negligible [13]. Therefore, implanted gold marker detection is a reliable method for repetitive position verification.

Although the use of gold markers is increasingly common, the complication rates have not been reported in a large patient population. The goals of this study were to report on the complication rate in patients with localized prostate cancer in whom gold markers were implanted transrectally and to identify the risk factors for the complications.

Methods and Materials

Patients and gold marker implantation

In all patients referred for RT for localized prostate cancer (Stage T1-T3N0M0), gold marker implantation was performed in the urology outpatient clinic. No preceding enema or anesthesia was used. A prophylactic antibiotic, ciprofloxacin 500 mg twice daily, for 3 days, was given. Anticoagulant medication was stopped 3–7 days before marker implantation.

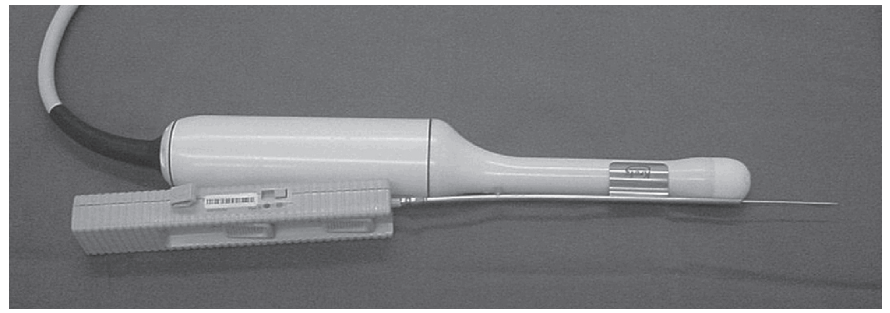
Patients were placed in the lateral decubitus position. First, the urologist measured the prostate volume with an ultrasound Kretz Voluson 530D device (GE Kretz, Zipf, Austria) with an endorectal transducer. Next, the gold markers were placed, under ultrasound guidance, with a standard 18-gauge prostate biopsy tool (Microvasive Topnotch, Boston Scientific, Natick, MA) mounted onto the endorectal ultrasound transducer (Fig. 1a). Fine gold markers 1 mm in diameter and 7 mm in length were used (Hospimed International BV, Dalfsen, The Netherlands; Fig. 1b). The length was chosen because of visibility on the portal images, CT scans, and MRI scans. Two markers were placed on the left and right at the base, one in the central part next to the urethra, and one at the apex of the prostate. After at least 1 week, to allow the swelling of the gland to resolve after implantation, the planning CT scan (3-mm slice thickness) was obtained. In Fig. 1c, an example of a portal image showing the implanted markers is displayed.

Complications and risk factors

All patients received a questionnaire from a research nurse after the implantation regarding any complications after marker implantation. This questionnaire was completed in the patient's home and returned to the nurse. The questionnaire asked for the presence or absence of hematuria, hematospermia, rectal bleeding, fever, and pain. Specifically, questions regarding the daily frequency of symptoms and total duration in days were included. Patients were also asked to report other complaints, symptoms, and additional medications (including names, dosages, duration, and effects) taken after implantation. Pain was scored on a 0–10 scale (0, no pain to 10, the worst pain imaginable). Patients were asked to compare the pain experienced during marker implantation with the pain experienced at the diagnostic prostate biopsy procedure. In cases of problems with the questionnaire or general problems, patients were instructed to contact the nurse.

Minor complications were defined as side effects with transient minimal discomfort and requiring no additional medical intervention. The complications that resulted in moderate discomfort and required additional treatment were considered moderate complications.

In most cases (184 of 209), the questionnaires were sent to the patients by mail



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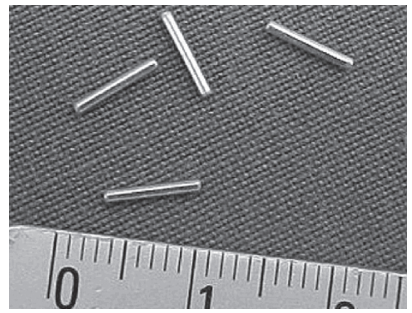

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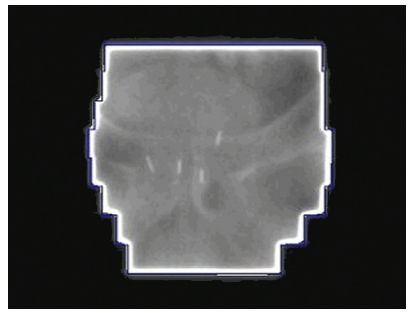

(c)

Figure 1

(a) Marker implantation tool, mounted on ultrasound probe.

(b) Fine gold markers.

(c) Portal image of anteroposterior radiotherapy treatment beam, with four implanted gold markers in situ.

after marker implantation. For this particular retrospective analysis, inconsistencies were verified with the patient by the nurse and researchers. The notes made by the urologist or radiation oncologist during marker implantation were checked retrospectively, and all other occurring complications were noted.

Possible risk factors for developing any moderate or any bleeding complications (e.g., hematuria, hematospermia, or rectal blood loss) were evaluated by reviewing the medical charts. The tumor stage, urologist performing the marker

implantation, use of anticoagulant therapy, previous transurethral resection of the prostate, previous prostatitis, presence of diabetes, prednisone use, patient age, duration of hormonal therapy, and prostate volume were recorded.

Statistical analysis was performed using t tests to compare continuous variables and Fisher's exact test (2 × 2 tables) or chi-square test (3 × 3 tables) to compare categorical variables. A *P* value of < 0.05 was considered statistically significant. To analyze the effect of the retrospective analysis, the patients who received the questionnaire directly after the procedure were evaluated separately and the outcomes were compared with the data obtained retrospectively.

Results

Patients and gold marker implantation

Between January 2001 and September 2005, gold markers were implanted in 236 patients. The mean age was 70 years (range, 40–84 years). Of the 236 patients, 27 were lost to follow-up because of death (n=9) or other factors (n=18). For 209 patients, the toxicity outcome could be analyzed, and the results reported concern this group of 209 patients. Of these 209 patients, the tumor was Stage T1 in 18, T2 in 64, and T3 in 127.

In 8 patients, marker misplacement outside the gland boundaries was observed during the treatment planning CT scan. This occurred seven times into the bladder and once into the rectum. On average, the whole implantation procedure took 10 minutes. Of the 209 patients, 79 were receiving anticoagulant therapy: acetylsalicylic acid (n=64), acenocoumarol (n=12), or other (n=3). Hormonal therapy was started in 202 patients, mainly before marker implantation, with a mean interval of 7 weeks (range, 0–40) until the procedure. The mean interval between implantation and the start of RT was 26 days (range, 10–49 days). The encountered complications did not cause a delay in the start of RT in any patient. The prostate volume was 5–136 cm^3 (mean, 40). None of the investigated patients complained of rectal bleeding or other symptoms of inflammatory bowel disease before marker implantation. For the retrospective complications analysis, the

Table 1

Complication rates.

Complication	Patients	(%)
Minor		
Hematuria > 3 d	8	(3.8)
Hematospermia*	15	(18.5)
Rectal bleeding	19	(9.1)
Voiding complaints	4	(1.9)
Moderate		
Pain requiring analgesics	6	(2.9)
Fever	4	(1.9)
Nausea/vomiting	2	(1.0)
Allergic reaction to antibiotic	1	(0.5)

Data in parentheses are percentages.

* Of 81 patients reporting ejaculations.

questionnaire was completed at a mean of 90 weeks after marker implantation.

Complications and risk factors

In Table 1, the observed complication rates are listed. No statistically significant differences in any of the complications were found between the patients who answered the questionnaire directly after the procedure and those patients who performed this later (data not shown).

Minor complications

In all cases, hematuria was self-limiting within 7 days. Hematospermia was noted by 15 of the 81 patients who reported having had ejaculations. The average duration of rectal bleeding was 2.5 days. In 13 of 19 patients, the rectal bleeding lasted for 1

Table 2

Risk factors and complication rates (Fisher's exact test)

Risk factor	Bleeding complication (%)		p	Moderate complications (%)		p
Tumor stage						
T1	5.6	(1/18)	0.026*	0	(0/18)	0.57*
T2	9.4	(6/64)		6.3	(4/64)	
T3	22.8	(29/127)		5.5	(7/127)	
Anticoagulant						
Yes	20.3	(16/79)	0.45	5.1	(4/79)	1.00
No	15.4	(20/130)		5.4	(7/130)	
TURP						
Yes	3.7	(1/27)	0.054	0	(0/27)	0.37
No	19.2	(35/182)		6	(11/182)	
Prostatitis						
Yes	16.7	(2/12)	1.00	8.3	(1/12)	0.49
No	17.3	(34/197)		5.1	(10/197)	
Diabetes						
Yes	22.2	(4/18)	0.52	0	(0/18)	0.60
No	16.8	(32/191)		5.8	(11/191)	
Prednisone						
Yes	0	(0/1)	1.00	0	(0/1)	1.00
No	17.3	(36/208)		5.3	(11/208)	

Abbreviation: TURP = transurethral resection of prostate.* = Chi-square test.

Table 3

Risk factors and complication rates (t test).

Complication	Mean age (y)	Mean duration of hormonal therapy (wk)	Prostate volume (cm^3)
Bleeding			
Yes	68	4.4	43
No	71	7.2	39
p	0.022	0.028	0.38
Moderate			
Yes	71	5.1	46
No	70	6.8	39
p	0.85	0.51	0.11

day. One patient reported repeated minor blood loss during 21 days. The voiding complaints consisted of either an increase of previous complaints or dysuria.

Moderate complications

For the patients with a moderate complication, no admission to the hospital was necessary. Patients with fever received additional antibiotics, and their temperature normalized within a few days. The patient with the allergic reaction to ciprofloxacin recovered after termination of this antibiotic.

Pain

The mean pain score was 3.2 (range, 0–9). Of the 209 patients, 48% scored the pain as 0–2, 37% as 3–5, and 15% as 6–9. Also, 50% of the patients reported that the marker implantation procedure was less painful than the prostate biopsy procedure, 40% recorded comparable pain, and 10% noted more pain.

Risk factors

Significantly increased bleeding complications were seen in patients with advanced tumor stage, younger age, and shorter duration of hormonal treatment (Tables 2 and 3). The use of anticoagulants yielded no increase in rectal bleeding or other complication rates. None of the investigated risk factors correlated significantly with any moderate complication.

Discussion

In this study, the complications and risk factors were studied after transrectal implantation, under ultrasound guidance, of gold markers for position verification during prostate cancer RT. This is the first study reporting the marker-induced toxicity of a large patient group. Minor complications such as hematuria and hematospermia were observed in 3.8% and 18.5% of the patients, respectively. Rectal bleeding was seen in 9.1% of the patients and lasted for an average of 2.5 days. Henry et al. [14] reported on 12 patients in whom gold markers were implanted transperineally. Three patients noted hematuria, one hematospermia, and one rectal bleeding that occurred after the marker was most likely implanted through the rectal wall. No infections were seen. The transperineal route is thought to result in less rectal bleeding than the transrectal route. In the study by Henry et al., the duration of hematuria was not mentioned. Maximally, three markers were implanted, which could have been a factor in causing less rectal bleeding or hematospermia. Henry et al. [14] reported severe pain during implantation in 3 patients and 1 patient needed analgesics. A comparison with our results was difficult because of the difference in patient numbers. The second study that reported on implanted marker toxicity was of 10 patients, with a maximum of three fiducial markers implanted under ultrasound guidance [7]. Three patients reported transient hematuria the first 24 hours after implantation and seven reported an episode of rectal bleeding. Again, a comparison with our results was difficult because we only reported hematuria that lasted for > 3 days. In their study, the occurrence of hematospermia was not reported, and no moderate or major complications were observed.

Owing to the lack of reports on complication rates after marker implantation, a comparison was done with the complications occurring after prostate biopsy, although one should realize this procedure is performed for other purposes and under different circumstances and, therefore, the data are not fully comparable. After prostate biopsy, the incidence of minor complications (i.e., hematuria and hematospermia) has been reported at 64–78% [15-18]. Moderate complications, mostly infections, are seen infrequently, with a maximal rate of 4% [15,19]. Two studies noted a rate of 23% of hematuria lasting > 3 days, a rate of 45% for hematospermia, and a rate of 1.7% for rectal bleeding [20,21]. The range of rectal bleeding complications after prostate biopsy is wide (1.3–37%), with an average of 9.0% [16,18-23], comparable to our rates. We have no suggestion on how to reduce the rates we have reported, except for possibly reducing the number of implanted markers. We chose four markers to implant for reasons of redundancy and the certainty of visibility. With our present experience, we believe that geometric accuracy can be maintained with three markers. After prostate biopsy, the percentage of voiding complaints has varied from 1% to 12% [18, 21-23].

In some studies of transrectal ultrasound and transrectal prostate biopsy, minor or no discomfort was reported in up to 92% of patients and patient acceptance has been high [18,19]. However, studies have also reported severe discomfort in up to 30% of patients [16]. Irani et al. [24] evaluated 81 patients undergoing prostate biopsy. They found a mean pain score of 3, but 16% had significant discomfort (score > 5). We found similar results, with a mean pain score of 3.2 and 15% of patients having severe pain during implantation. Only 6 of the patients who reported pain needed analgesics. One-half of the patients reported that the marker implantation procedure was less painful than the diagnostic biopsy. This might be because only four markers were implanted in contrast to the multiple (six to eight) biopsy cores taken. Furthermore, the uncertainty of the diagnosis during the biopsy procedure could play a role in patients experiencing more pain.

Only 1.9% of our patients had fever after marker implantation, less than most others reported after prostate biopsy [15,16,18-23]. It was shown that an antibiotic prescribed for 3 days and started 1 day before the prostate biopsy reduced the number of infectious complications [15]. We also started ciprofloxacin 1 day before marker implantation and continued it for 3 days. Two patients had nausea and

vomiting after implantation. This could be a consequence of the procedure and a manifestation of bacteremia [23]. These patients, however, did not have fever, and the complaints resolved spontaneously.

Anticoagulant medication was stopped 3–7 days before implantation. As a result, no extra or longer bleeding complications occurred in this group. We have shown that patients with advanced tumor stage, younger age, and a shorter duration of hormonal treatment had significantly more bleeding complications. In these patients, increased prostatic vascularization might have played a role. This could be explained by the testosterone dependency of normal prostatic tissue growth and prostate cancer. In vivo studies have shown that androgen withdrawal leads to increased angiogenesis inhibitor production and decreased vascularization in the normal rat prostate. In human androgen-dependent prostate cancer, the expression of angiogenesis inhibitor correlates inversely with blood vessel density [25]. The growth and spread of prostate cancer in the elderly is often prolonged, and studies on mice have shown that the tumor growth rate is altered with older age because of the reduced capacity to vascularize tumors owing to a lack of angiogenic factors or the presence of host inhibitors [26]. It might be advisable to wait to perform implantation until shortly before RT, so that the hormonal therapy has caused a maximal reduction in the tumor volume and decreased vascularization. As we have experienced, a disadvantage of a smaller prostate can be technical difficulties in marker implantation. Studies have shown that younger patients experience more pain during prostate biopsies [16,18]. This could not be confirmed in our study. Raaijmakers et al. [21] have identified risk factors for complications after prostate biopsy. An earlier episode of prostatitis was associated with more pain and hospital admission. Prostate volume was a predictor of urinary retention. In our study, no specific risk factors for complications could be identified, and urinary retention did not occur in any of the 209 studied patients.

In each prostate cancer patient referred to our department, gold markers are implanted transrectally. The role of the markers in accurate position verification and correction has been well established [10-12,27]. Recently, the first clinical data have been published of a new type of implantable radiofrequency emitting device that continuously measures the position of the prostate during treatment [28]. Implantation

under ultrasound guidance of these markers, in size comparable to gold markers, also yielded no severe complications. In addition to verification purposes, we have been using the gold markers for high-precision magnetic resonance imaging-CT fusion and prostate delineation during the treatment planning process [29].

Conclusion

Transrectal gold marker implantation for prostate position verification is safe and appears to be a well-tolerated procedure. In only 1.9% of the studied patients were minor voiding complaints observed. Other minor transient complications, defined as hematuria lasting > 3 days, hematospermia, and rectal bleeding, occurred in 3.8%, 18.5%, and 9.1% of the implanted patients, respectively. These minor bleeding complications were more frequently seen in patients with an advanced tumor stage, younger age, and shorter duration of hormonal therapy. Moderate complications were rare (6.2%) and consisted mainly of pain and fever. These were treated with oral medication, which resolved the complaints quickly.

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Chapter

04

Technique and complications of postprostatectomy gold markers

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Chapter 4

Postprostatectomy ultrasound-guided transrectal implantation of gold markers for external beam radiotherapy: technique and complication rate

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Submitted

Abstract

Background and Purpose: Postprostatectomy radiotherapy offers survival benefit in adjuvant or salvage setting. The implantation technique and complication rate of gold markers in the prostate bed for high-precision radiotherapy is analyzed.

Material and Methods: Men undergoing postprostatectomy radiotherapy for PSA relapse or high-risk disease were enrolled. Under transrectal ultrasound guidance, three fine gold markers were implanted transrectally in the prostate bed and technical difficulties on insertion were documented. Patients received self-designed questionnaires regarding complications and pain. The influence of anticoagulants or coumarines on bleeding and potential risk factors on pain was analyzed.

Results: In 77 consecutive men, failure of marker implantation or migration was seen in 6 patients. Rectal bleeding was reported by 10 patients and voiding complaints by one. Hematuria occurred in only 12 patients for maximal 3 days. Other complications were rectal discomfort (n=2), nausea (n=1), abdominal discomfort (n=1), and pain requiring analgesics (n=4). No major complications were reported. The mean pain score was 3.7 on a 0–10 visual analogue scale. No clinical significant risk factors for complications were identified.

Conclusions: Transrectal implantation of gold markers in the prostate bed is feasible and safe. The potential advantages of marker implantation for high-precision postprostatectomy radiotherapy outweigh the minor risks.

Introduction

The implantation of intraprostatic gold markers for external beam radiotherapy (EBRT) of prostate cancer has become a standard technique for daily position verification and correction of patient setup errors and prostate motion [1,2]. A long-term experience with gold marker implantation has been reported recently [3], and complication rates were shown to be low [4]. With dose-escalation improved biochemical control rates are found [5,6]. With increasing doses, however, both delineation of the target volume and high-precision of dose delivery are important to prevent increased toxicity to surrounding organs [7].

Radiation therapy after radical prostatectomy offers an overall or biochemical relapse-free survival benefit when applied in an adjuvant or salvage setting [8-10]. In contrast with the published data on prostate motion [11-14], few data exist on patient setup uncertainties and prostate bed motion during postprostatectomy radiotherapy [15-17]. To our knowledge, the use of gold markers in this setting has been described only twice [16,17]. According to Ost et al. [18], the prostate bed motion is similar to the intact prostate gland motion. Daily electronic portal imaging of gold markers may be a valuable method to correct for interfraction target motions and to improve precision in EBRT delivery [16]. The correction of target positioning errors is especially critical when small prostate bed-only fields are irradiated. Small shifts of target volume have the potential to significantly alter the dose distribution delivered to adjacent organs.

The side effects of postprostatectomy gold marker implantation may differ from those after implantation in the highly vascularized prostate gland. Theoretically, less bleeding complications may occur. However, the anatomic changes may prevent recognition of the implantation site and make the procedure technically more challenging. As the anastomosis is located distally in the pelvis this may lead to misplacement of markers or pain during implantation. Due to fibrosis around the bladder-urethra anastomosis pain may be more prominent. Therefore, the aim of this study is to evaluate the technique and complication rate of postprostatectomy transrectal implantation of gold markers, and to analyze potential risk factors for complications.

Materials and Methods

Technique of gold marker implantation

During the study period, in all patients with PSA relapse or high-risk prostate cancer, i.e. pT3 and/or positive surgical margins after radical prostatectomy, gold marker implantation was performed in an outpatient setting of two referral centres. No preceding enema or local anesthesia was used. Ciprofloxacin 500 mg twice daily was given as prophylaxis, for 3 days. Anticoagulant therapy was continued in one centre (Radboud University Nijmegen Medical Centre, RUNMC), based on the low bleeding risk after intraprostatic gold marker implantation [4], or stopped for a week (Medical Centre Alkmaar, MCA). Coumarines were stopped 3 days in advance with INR < 2.0 during marker implantation. Patients were placed in the lateral decubitus (RUNMC) or dorsal lithotomy position (MCA) for the procedure. The transrectal ultrasound (TRUS) -guided gold marker implantation was performed by two physicians (JAW, RD), with a B-K Medical Pro Focus 2202 (B-K Medical, Herlev, Denmark) or a B-K Medical Falcon 2102 EXL ultrasound device (B-K Medical, Wilmington, USA). Three fine gold markers, 1.2 mm in diameter and 5 mm in length, preloaded in needles (QLRAD, Zwolle, the Netherlands) were implanted. A standard length of markers was chosen because of visibility on portal images and planning CT scans (3-mm slice thickness). Two markers were placed at the right and left dorsal bladder base, and one next to the anastomosis. The implantation was performed at least two weeks before the planning CT scan, for prostate bed edema to resolve. With portal imaging and planning CT scans the migration or loss of gold markers from the prostate bed was recorded.

Complication registration

The patients received questionnaires directly after the implantation procedure and filled them out during the first week. A group of patients that already had the markers implanted received the questionnaires by mail for retrospective analysis. All patients were contacted by one of the researchers (JFL), to clear any inconsistencies and to clarify details of medical history that could not be extracted from the medical charts. As no validated questionnaires for this procedure exist, a self-designed questionnaire was used regarding complications that are commonly described after prostate biopsy and intraprostatic gold marker implantation

procedures, containing the following items: presence of hematuria, rectal bleeding, fever, pain, voiding problems or any other complaints. The frequency and duration of symptoms, and the need for medication (names, dosages, duration, and effects) were evaluated. Patients reported if the implantation was bothersome and scored the pain on a 0–10 visual analogue scale (0, no pain; 10, worst pain imaginable). Patients were asked to compare the pain with the pain that they had experienced after diagnostic prostate biopsies. Complications were defined as: minor, for transient minimal discomfort without medical intervention; moderate, for moderate discomfort or requirement of additional treatment; major, when hospital admission was necessary. To analyze any bias in complication registration, the retrospectively gathered data were compared with the prospective data.

Potential risk factors for complications were evaluated by reviewing the medical charts and by contacting all patients. The primary hypothesis was that the use of anticoagulants and/or coumarines could be a risk factor for bleeding. A secondary hypothesis was that local tumor infiltration and wider surgical excision, the surgical technique itself, and strictures, for which endodilatation or bladder neck incision were necessary or incontinence may have stimulated fibrosis formation and more pain during marker implantation. Therefore, the initial pathological tumor stage, the surgical technique, the presence of incontinence or strictures, the time interval since surgery, and the age were evaluated for their influence on pain during the procedure.

Statistical analysis of bleeding complications was performed using Fisher's exact tests to compare categorical variables. Differences in VAS scores by potential risk factor were tested for statistical significance by using the parameter free Mann-Whitney U test for 2 groups or the Kruskal-Wallis test for 3 groups. The correlation between continuous variables and the VAS pain scores was quantified with Spearman correlation coefficients (SPSS 16.0 for Windows (© SPSS Inc., 1989-2005)). A two-sided P value < 0.05 was considered statistically significant.

Results

Between February 2008 and February 2011, gold markers were implanted in 77 consecutive men with PSA relapse (n=70) or high-risk disease (n=7) after radical prostatectomy. All patients during this period were included in the study. The mean age was 65 years (range, 54–77). Patients had been operated by open radical (n=48), laparoscopic (n=10), or robot assisted laparoscopic radical prostatectomy (n=19). The pathological tumor stage was T2 (n=33), T3 (n=43), or T4 (n=1). The mean time interval since surgery until marker implantation was 29 months (range, 2–147). The mean time interval between marker implantation and EBRT was 3.8 weeks (range, 2–19). The encountered complications did not cause any delay of radiotherapy. Twelve patients were on anticoagulant therapy, 4 on coumarines and one on both. No inflammatory bowel disease was present before marker implantation, but one patient suffered from rectal bleeding due to hemorrhoids. Forty-one patients filled out the questionnaires retrospectively, at a mean 18 months (range, 3–36) after marker implantation.

Feasibility of gold marker implantation

In one patient a substitute gold marker was placed because misplacement into the bladder wall was observed during TRUS. In another patient marker placement failed due to an empty bladder and the procedure was performed successfully one week later. Because the anastomosis was located very distally in one patient, only

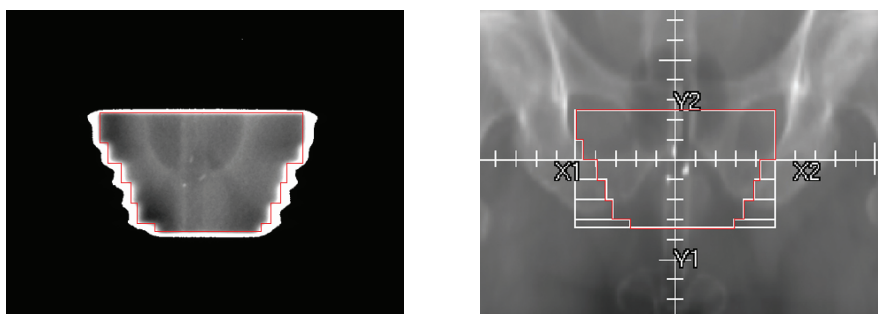

Figure 1

Anterior portal image of three gold markers in prostate bed.

Table 1

Complication rate after gold marker implantation in the prostate bed.

Complication	Patients (%)	
Minor		
Hematuria > 3 days	0	(0%)
Rectal bleeding	10	(13%)
Voiding complaints (urgency)	1	(1%)
Moderate		
Pain requiring analgesics	4	(5%)
Rectal discomfort	2	(3%)
Fever	0	(0%)
Nausea	1	(1%)
Other	1	(1%)
Major	0	(0%)

two markers could be placed. Bleeding was observed during the procedure with TRUS in one patient. The physicians noticed technical challenges with implantation of most of the distal markers, because of the steep angle of the ultrasound probe and fibrosis. In 3 patients, a marker was missing on planning CT scan. In general, gold markers were easily distinguishable from surgical clips on portal images. Figure 1 shows an example of an anterior portal image of gold markers.

Complications

The complication rate of 76 patients could be analyzed because one patient was lost to follow-up after emigration (Table 1).

Minor complications

No hematuria > 3 days occurred, but 12 patients had hematuria for 1 day, two for 2 days, and one patient for 3 days. Rectal bleeding was always self-limiting within

Table 2

Potential risk factors for bleeding complications after gold marker implantation in the prostate bed (Fisher's exact test).

Risk factor	Bleeding complication % (n)		*P*-value
Use of anticoagulant or coumarine			
Yes	44	(7/16)	
No	23	(14/60)	0,12
Anticoagulant stopped before marker implantation			
Yes	14	(1/7)	
No	80	(4/5)	0.072

a day. No significant differences in bleeding incidence occurred between the prospective and retrospective groups (36% and 20%, respectively; Fisher's exact test: $P = 0.13$).

Moderate complications

One patient reported nausea for 2 days. Rectal discomfort lasted for 1 day (n=1) or 1 week (n=1) after implantation, and required no analgesics. One patient reported abdominal discomfort and diarrhea for a week. No major complications occurred.

Pain

Twenty-five patients (33%) considered the procedure bothersome and the mean VAS score was 3.7: 41% scored the pain as 0–2, 37% as 3–5, and 22% as 6–10. No significant differences were seen between prospective and retrospective groups (data not shown). The procedure was experienced as being less painful than prostate biopsies by 43%, comparable by 38%, and more painful by 16%. Two patients (3%) had no previous biopsies.

Table 3

Potential risk factors for pain measured by Visual Analogue Score (VAS) during marker implantation in the prostate bed.

Risk factor		Median VAS score (IQR)		*P*-value
Pathological tumor stage				
T2	(33/76)	3.3	(5.0)	
T3-4	(43/76)	5.0	(5.0)	0.087
Surgical technique				
OP	(47/76)	3.5	(5.0)	
LP	(10/76)	5.0	(4.0)	
RALP	(19/76)	4.3	(5.0)	0.595
Incontinence				
Yes	(35/76)	5.0	(5.0)	
No	(41/76)	3.3	(3.5)	0.360
Stricture				
Yes	(11/76)	5.0	(5.0)	
No	(65/76)	3.5	(3.5)	0.893
		Spearman correlation coefficient		
Age		-0.19		0.097
Time interval since surgery		-0.09		0.458

IQR=interquartile range; OP=open prostatectomy; LP=laparoscopic prostatectomy; RALP=robot assisted laparoscopic prostatectomy

Potential risk factors

In Tables 2 and 3, the potential risk factors are shown. In patients who stopped anticoagulants, a trend was seen for less bleeding compared to those who continued anticoagulants (14% and 80%, respectively ($P = 0.072$)). Old patients showed a trend of less pain than the younger ones. Extensive surgery and anastomotic strictures did not increase pain during marker implantation.

Discussion

In this study, the ultrasound-guided transrectal implantation of gold markers for postprostatectomy radiotherapy appeared feasible with a low complication rate. Moman et al. [3] showed the feasibility, side effects, and QOL of transrectal and transperineal intraprostatic implantation of gold markers in 914 patients. Marker migration led to discontinuation of marker-based IMRT in 5 patients. One marker was lost and marker displacement ranged from 3 to 4 mm. In general, migration of intraprostatic markers is negligible. One report about marker migration in the prostate bed showed an interfraction variation of intermarker distance of 0.4 mm to 0.9 mm [16]. The authors concluded that gold markers can serve as reliable fiducials to mark the target volume over the course of salvage or adjuvant EBRT. In our series, difficulties in marker placement occurred in 3 patients and markers were missing on planning CT scan in another 3 patients. Alternative alignment procedures were necessary and interfraction prostate bed motion could not be assessed. Discrimination between gold markers and surgical clips on imaging has been suggested to be difficult [18]. This was not experienced by our radiation oncologists.

This is the first report specifically evaluating complications of gold marker implantation in the prostate bed. No hematuria > 3 days was found and rectal bleeding was self-limiting within one day. In a large patient group, hematuria > 3 days was reported in 3.8%, and rectal bleeding in 9.1% for an average 2.5 days after intraprostatic gold markers [4]. Others have found similar complication rates, in smaller series, for both transrectal and transperineal intraprostatic marker implantation [19,20]. Moman et al. [3] found hematuria in 39% and rectal discomfort in 8% of patients after transrectal intraprostatic markers. Only 0.5% of patients had grade 3 toxicity (urosepsis). No urosepsis was found in our patients, possibly because of less vascularization compared to the prostate gland and low potential of systemic spread of bacteria. Also, pathological exams often show infectious focus of the prostate gland. The lower incidence of hematuria than after prostate marker implantation may be explained by the fibrosis of the prostate bed. The anastomosis was clearly visible during TRUS-guided marker implantation, provided the bladder was not empty, and the chance of urethra perforation and hematuria

was therefore low. The somewhat higher occurrence of rectal bleeding may be due to the distal placement of markers and the steep angle of the transducer with traction on the rectal wall. Because bleeding was minor and self-limiting when using anticoagulant medication, this therapy should be continued in patients with high-risk for thrombo-embolic events. Although a trend was observed, our primary hypothesis of higher bleeding risk with anticoagulants use was withdrawn. The INR should be kept < 2.0 for safety reasons. Few moderate complications occurred, but one patient reported nausea which could have been caused by bacteremia or ciprofloxacin use.

Most patients had undergone diagnostic prostate biopsies, possibly leading to a higher level of acceptance of gold marker implantation. In a study with differentiated QOL assessments for intraprostatic gold markers, no significant differences between pre- and post-implantation measurements were found [3].

Concerning the secondary hypothesis about risk factors, the influence of strictures after radical prostatectomy on pain during marker implantation was evaluated. It has been suggested by others that anastomotic leakage may lead to excessive fibrosis and stricture formation [21]. Some men who develop anastomotic strictures may even have a generalized tendency to develop a hypertrophic scar [22]. These patients may have more pain during marker implantation in rigid fibrotic tissues. In our series, the hypothesis that extensive surgery and strictures may increase the pain was not confirmed. The marker implantation was bothersome in 30% of patients, with an average VAS score of 3.7. This is somewhat higher than in our previous study when 4 intraprostatic gold markers were implanted [4]. Although fewer small markers were implanted, the steep angle of the ultrasound transducer, especially with implantation of the distal marker, and fibrosis may have caused more pain. The prophylactic use of analgesics can therefore be advocated, especially in young patients.

The shortcomings of this study are that the questionnaires were completed retrospectively by 41 patients, which may have caused underreporting of complications due to a recall bias, although no significant differences were seen compared with the rest. Due to the sample size, the number of uncommon serious

side effects (e.g. profuse rectal bleeding or urosepsis) may also be underestimated. Further, no VAS score was recorded during prostate biopsy procedures making the comparison with the marker implantation procedure less reliable.

In our centres, the TRUS-guided transrectal implantation of gold markers for postprostatectomy radiotherapy is standard care. Although it should be realized that the implantation of gold markers is an invasive procedure, which may potentially lead to serious complications, in our experience, the complication rate is negligible. Future research should focus on clinical outcome, i.e. tumor control rate and normal tissue toxicity, in patients receiving postprostatectomy radiotherapy with daily gold marker-based correction procedures.

Conclusions

Transrectal ultrasound-guided gold marker implantation in the prostate bed is feasible and safe. The complication rate is comparable to or even less than the complication rate observed after intraprostatic gold marker placement. The pain is slightly more prominent and may be caused by fibrosis, but extensive surgery and anastomotic strictures did not increase pain. The potential advantages of gold marker implantation for high-precision postprostatectomy radiotherapy outweigh the minor risks.

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Chapter

05

Clinical results of modern cryotechnology

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Chapter 5
Cryosurgery for prostate cancer: an update on clinical results of modern cryotechnology

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Abstract

Context: Cryosurgery is an evolving treatment for localized prostate cancer in European centers. Modern cryotechnology is associated with a low complication rate, but its definitive role in the spectrum of different treatment modalities remains to be determined.

Objective: The primary objective of this review is to analyze the oncological results and complication rates of modern cryosurgery for prostate cancer. Secondarily, the impact of patient selection and the criteria for treatment success are discussed.

Evidence acquisition: A structured literature review was performed by an online Pubmed search for data of primary and salvage cryosurgery of the prostate. Papers with relevant information on clinical outcome and complication rates were selected.

Evidence synthesis: The introduction of gas-based third-generation cryotechnology has significantly decreased side effects with similar oncological results compared to older techniques. The occurrence of severe complications like rectourethral fistulas (< 1%) has almost been eradicated, but the rates of erectile dysfunction remain high (90%). With salvage cryosurgery more side effects can be expected with an average incontinence rate of 8% and fistulas up to 3.4%. Nevertheless, this minimal invasive treatment remains an option for radiorecurrent prostate cancer. Focal cryosurgery is considered experimental, but is an interesting new development in cryosurgery. The intermediate-term biochemical disease free survival rates of 60%–90% are comparable to the results of other treatment modalities. However, the current data of cryosurgery in literature are of low-level evidence which should be discussed when counselling patients.

Conclusions: Modern cryosurgery is reliable and results are promising with minimal morbidity. Focal cryosurgery in selected patients aims to reduce side effects, but is currently experimental treatment. Randomized trials comparing the outcomes of the different treatment modalities and long-term follow-up data are needed to define the ultimate role of cryosurgery in the treatment of localized prostate cancer.

Introduction

Cryosurgery for prostate cancer was first applied in 1964 by Gonder et al. using liquid nitrogen [1]. The technique encompassed transurethral freezing of the prostate with the inability to position the cryoneedles precisely and to monitor the extent of freezing. This resulted in severe and frequent complications such as incontinence, urethral sloughing and rectourethral fistulas. Therefore, cryosurgery of the prostate was abandoned until the late 1980s, when Onik et al. [2] refined the technique by using interventional radiologic procedures and transrectal ultrasound (TRUS). The accurate TRUS-guided transperineal placement of cryoprobes with real-time monitoring and control of the freezing process has significantly decreased the number of complications [3,4]. The use of a urethral-warming catheter decreased the sloughing rate of the urethral mucosa and subsequently the risk of obstructive problems [5,6]. Consequently, cryosurgery was recognized by the American Urological Association (AUA) as a therapeutic option for localized prostate cancer in 1996.

Since the use of thermosensors in Denonvilliers' fascia and nearby the neurovascular bundles [7] and the application of gas-based cryosurgery [8], complication rates have further decreased. The introduction of argon gas for freezing and helium gas for thawing, permitted a dramatic reduction in the diameter of the cryoprobes. The ultrathin 17-gauge (1.47mm) cryoneedles have a very sharp tip, that allows for a direct transperineal placement into the prostate [9]. The cryoneedles are inserted through a brachytherapylike template and because of the smaller diameter more needles can be placed. This enables a precise contouring of the ice ball, subsequently resulting in a more effective ablation of the gland. The track dilatation and insertion kit, that were needed for older generation cryoprobes (3.5–5.5mm),

are no longer necessary [9-11]. This development has significantly minimized the scrotal swelling and perineal ecchymosis occurring after the procedure [12]. By active instead of passive warming the procedure can be performed much quicker which is advantageous for the patient's recovery. Most patients are discharged from the hospital either the same day or the following day after treatment [13].

These technical improvements have made modern cryosurgery a minimal invasive procedure. Most reports in the literature are from the USA and Canada, but cryosurgery is evolving in European centers [13,14]. Therefore, an update is provided of the latest results of modern cryosurgery as a primary treatment option or as a salvage procedure for radiorecurrent prostate cancer. We specifically discuss the impact of patient selection and criteria of treatment success on the oncological results. Also, developments such as focal- and nervesparing cryosurgery are discussed.

Evidence acquisition

The aim of this review is to put the results of third-generation cryosurgery in perspective with older techniques. Therefore, a structured literature review was performed by an electronic Pubmed search from January 1960 until June 2008. Data of primary- and salvage cryosurgery of the prostate with the following search terms: 'cryosurgery and prostate cancer' (rendering 426 articles), 'cryotherapy of the prostate and prostate cancer' (rendering 83 articles) and 'cryoablation and prostate cancer' (rendering 446 articles) were retrieved. We only selected papers with relevant information on clinical outcome and treatment-induced complication rates. As data on overall survival and cancer-specific survival were lacking in most studies, predominantly biochemical disease-free survival (bDFS) rates were included.

We applied the following criteria for identification of articles to be clinically relevant:

- English language.
- Original papers with the elimination of review articles.

- Screening of reports for overlap of patient data by checking the center of treatment, co-authorship and time frame of patient selection.
- Any report of third-generation gas-based cryosurgery.
- A few large series on older techniques with a minimum of 12 months follow-up.

Evidence synthesis

Primary cryosurgery of the prostate

In most studies with intermediate-term follow-up both liquid nitrogen- and gas-based cryosurgery techniques have been used. In general, these show an actuarial biochemical disease-free survival (bDFS) of 60%–90% at 7 years [15,16]. Long-term overall survival data have not been published yet and one report shows a 5-year overall survival of 89% [17]. The bDFS for gas-based third-generation cryosurgery is comparable to the results in previous reports of older techniques [12,14,18]. Table 1 summarizes the results of recently published series, concerning primary cryosurgery of prostate cancer.

Clinical outcome

The PSA value is often used as a surrogate endpoint for treatment success in cryosurgery. The PSA-based definition of biochemical failure in literature varies considerably, complicating the comparison of outcomes. For instance, Long et al. [16] performed a retrospective outcome analysis of a database of 975 patients from five institutions, who underwent cryosurgery as primary treatment for localized or locally advanced prostate cancer. The median follow-up was 24 months. Using a PSA threshold of < 0.5 ng/ml and < 1.0 ng/ml, the 5-year actuarial bDFS ranged from 36%–61% and 45%–76%, respectively, depending on risk category of the patients. Bahn et al. [15] retrospectively reviewed a series of 590 patients, with a mean follow-up of 5.4 years. This data set of patients was also used by Long et al. [16]. Using a PSA threshold of < 0.5 ng/ml, they found a 7-year actuarial bDFS for low-, intermediate- and high-risk patients of 61%, 68% and 61%, respectively. For a PSA threshold of < 1.0 ng/ml the respective bDFS rates were 87%, 79% and 71%. However, using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical failure (three successive increases

of PSA level), the bDFS was 92%, 89% and 89%, respectively. The outcome of the largest database for primary cryosurgery [19] shows a 5-year actuarial bDFS of 77% according to the ASTRO criteria, for mainly intermediate to high risk patients. This Cryo On Line Data (COLD) Registry encompasses assembled results from academic and community centers. A significant overlap in patient data exists with previously reported papers (Table 1).

Uniform criteria for treatment success are currently not agreed upon, but the combination of a static threshold with the need for a rising PSA trend with time seems reasonable. For instance, Shinohara et al. [20] evaluating 110 patients after cryosurgery for prostate cancer defined biochemical disease recurrence as a subsequent rise in PSA of > 0.2 ng/ml from nadir. Patients with a PSA nadir of < 0.1 ng/ml had a 7% biopsy failure rate. Those with nadir values of 0.1 to 0.4 ng/ml had 22% biopsy failures. Patients with a PSA nadir of ≥ 0.5 ng/ml had 60% biopsy failures. Apparently low PSA levels must be achieved after cryosurgery and therefore they suggested a threshold value of PSA ≤ 0.4 ng/ml for defining a successful outcome.

Although cryosurgery is an ablative therapy, detectable levels of PSA are not necessarily associated with persistence of cancer cells, because there is usually preservation of some tissue surrounding the urethra that can be benign and may release PSA. Thus, the definition of treatment success that is just on the threshold of PSA detection (PSA < 0.1 ng/ml) may be unreasonable to apply for cryosurgery.

In radiotherapy the ASTRO definition is accepted, but because this is a tumour selective therapy targeting dividing over non-dividing cells it is unknown whether it can apply to cryosurgery as well. It is also questionable whether the newer

Table 1 Results of primary cryosurgery

Ref. (with actuarial data)	No. patients	Median follow-up in months (range)	Technique	PSA threshold	b DFS (%) Low risk	Intermediate risk	High risk [a]	nADT (%)	Duplication data [b]: y/n (reference)
Long et al. [16] (5-year data)	975	24 (SD ± 16.5)	LN/Ar	< 0.5 < 1.0	60 76	61 71	36 45	33	y (15)
Donnelly et al. [17] (5-year data)	76	61 (35-85)	LN	< 0.3 < 1.0	60 75	77 89	48 76	34	y (19)
Bahn et al. [15] (7-year data)	590	68 (NA)	LN/Ar	< 0.5 < 1.0 ASTRO	61 87 92	68 79 89	61 71 89	91	y (16,19)
Ellis et al. [65] (3-month data)	75	3 (NA)	Ar	< 0.4	84 (all risk groups)			NA	n
Han et al. [12] (1-year data)	122	12 (NA)	Ar	< 0.4	78	NA	71	37	n
Cytron et al. [66] (NA)	23	11 (mean) (9-18)	Ar	< 0.5	78 (all risk groups)			NA	n
Prepelica et al. [18] (6-year data)	65	35 (4-77)	Ar	ASTRO	83 (most high risk)			68	y (19)
Creswell et al. [14] (1-year data)	31	9 (1.5-18)	Ar	< 0.5	60	NA	60	NA	n
Polascik et al. [67] (NA)	50	18 (3-43)	Ar	< 0.5	90 (all risk groups)			26	n
Jones et al. [19] (5-year data)	1198	24 (SD ± 26)	LN/Ar	ASTRO Phoenix	85 91	73 79	75 62	NA	y (15,17,18)
Hubosky et al. [68] (2-year data)	89	11 (1-32)	Ar	< 0.4 ASTRO	74 94 (all risk groups)	70	60	35	n
Cohen et al. [62] (10-year data)	204	12.6 (9.7-15.0)	LN	ASTRO Phoenix	56 (all risk groups) 81	 74	 46	0	n
Chin et al. [23] (4-year data)	33	19 (NA)	Ar	ASTRO Houston	13 (all risk groups) 36 (all risk groups)			100	n

Table 1 >>

a) d'Amico risk stratification (1992 American Joint Committee on Cancer): low risk = PSA < 10 ng/ml and Gleason biopsy ≤ 6 and clinical stage T1c-T2a; intermediate risk = PSA 10-20 ng/ml or Gleason biopsy 7 or clinical stage T2b; high risk = PSA > 20 ng/ml or Gleason biopsy ≥ 8 or clinical stage ≥ T2c; nADT, neoadjuvant androgen deprivation therapy.
b) Duplication of reporting some patient data likely: yes or no (reference).
NA, not available; SD, standard deviation; LN, liquid nitrogen; Ar, argon gas; bDFS, biochemical disease free survival; ASTRO = three successive rises in PSA; Houston/Phoenix = PSA 2 ng/ml above nadir.

Phoenix or Houston definition may be appropriate for prostate cryosurgery. According to this definition any increase of 2 ng/ml above the nadir value during follow-up is considered to indicate a biochemical recurrence [21]. Because a PSA nadir after prostate cryosurgery is typically achieved, unlike radiation, by 3 months after the procedure, the use of this definition may be reasonable. Lacking uniform criteria for treatment success we propose to define biochemical failure using a PSA threshold of 0.5 ng/ ml as well as the Phoenix/Houston definition.

Not only the PSA-based definitions of biochemical failure, but also a stratification of patients into risk groups determines the outcome. Success rates appear to be worse for high risk patients with a PSA > 10 ng/ml and Gleason scores > 7 [15,16]. However, a recent study [18] showed that even in the presence of a PSA ≥ 10 ng/ml and Gleason score ≥ 8, a favourable outcome could be achieved in 80% of patients. The numbers of patients in this study were low and these results should be interpreted cautiously. Besides, the results are probably influenced by concomitant hormonal therapy in 67% of patients. These patients generally have low serum testosteron levels for at least 2 months after cessation of treatment and therefore PSA levels after cryosurgery may be influenced by hormonal therapy.

From the early 1960s, cryosurgery was used as a treatment option for localized prostate cancer, that resulted in survival rates that approximated those of surgery and radiotherapy for all stages of disease [22]. Donnelly et al. [17] stated that the current treatment modalities for low-risk disease as watchful waiting, radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy achieve excellent local and systemic control. They compared the 5-year bDFS of these modalities to their cryosurgical results of a liquid nitrogen system for intermediate and high-risk patients, using PSA threshold values of < 0.5 ng/ml and < 1.0 ng/ml. The efficacy of cryosurgery appeared to be superior to both EBRT and three-dimensional conformed RT (3DCRT) for high-risk patients and to EBRT for intermediate-risk patients. Furthermore, the results of their series were comparable to radical prostatectomy as well as brachytherapy for intermediate and high-risk patients and to 3DCRT for intermediate-risk patients. Also the incontinence rates in this series compared favourably with the complications of the other treatment modalities. Although these results are encouraging, the patient numbers are

Table 2 Complications (%) after primary cryosurgery

Ref.	No. Patients	Tech-nique	Fistula	Slough	Reten-tion	Inconti-nence	Impo-tence	UTI	Peri-neal pain
Long et al. [16]	975	LN/Ar	0.4	NA	10	7.5	93	NA	NA
Donnelly et al. [17]	76	LN	NA	3.9	NA	1.3	100 (53: >3 yr)	NA	NA
Bahn et al. [15]	590	LN/Ar	0.004	NA	5.5	4.3	95	NA	NA
Ellis et al. [65]	75	Ar	0	6.7	6.7	5.4	82	NA	NA
Han et al. [12]	122	Ar	0	4.9	NA	3	87	NA	6
Prepelica et al. [18]	65	Ar	0	NA	3.1	3.1	NA	NA	3.1
Jones et al. [19]	1198	LN/Ar	0.4	NA	NA	2.9	91	NA	NA
Hubosky et al. [68]	89	Ar	1	2	4	2	NA	1	6

UTI, urinary tract infection; NA, not available; LN, liquid nitrogen; Ar, argon gas.

small making valuable comparison difficult and possibly inappropriate. Other studies confirm that the 5-year to 7-year bDFS and positive biopsy rates after cryosurgery are comparable to matching outcomes reported after EBRT, 3DCRT and brachytherapy with similar morbidity rates [15,16].

Despite the relative deficiency in patient numbers and trial design, in a randomized trial comparing third-generation cryosurgery with EBRT for locally advanced prostate cancer it was concluded that the results of cryosurgery were less favourable compared to those of EBRT and cryosurgery was considered suboptimal primary treatment in these patients [23]. Although the bDFS at 4 years was clearly in favour of EBRT (13% and 47%, respectively), the disease-specific and overall survival were identical. However, a major advantage of cryosurgery over radiation therapy is that it can be repeated for residual disease without increasing the side effects.

Complication rates

The current technology of primary cryosurgery has minimal severe side effects (Table 2). In the COLD Registry database [19] the incontinence rate necessitating the use of pads was 2.9%. Rectal fistulas occurred in 0.4% and impotence in 91%. Very early series of first-generation cryosurgery reported high rates of rectourethral fistulas which have been virtually eliminated by third-generation cryosurgery [14]. The morbidity that was reported in second-generation series of liquid nitrogen-based systems was mainly due to the use of older ultrasound equipment with less controllable freezing of the gland. This resulted in complications like urethral slough and retention in 10–23% and incontinence in 8–15% [24-26]. The temporal restriction by the US Food and Drug Administration on the type of urethral warming catheter that was used in 1994 was another important factor increasing the rates of slough [5,16]. Once the warming catheter was reintroduced to practice, the sloughing level decreased to the 4% that was seen just before 1994 [5]. As some studies have shown that 66% and 45% of prostate cancers is located within 5 mm and 1 mm from the urethra respectively, the increased risk of residual periurethral tumour due to sublethal periurethral temperatures caused by the use of a warming catheter should be taken into consideration [27]. The only adverse event that affects most patients (80–90%) nowadays is erectile dysfunction. Some reports suggest a recovery of sexual function, because the neurons for erectile function are not killed but injured and axonal regeneration after freeze injury may lead to functional recovery [28]. Despite this phenomenon cryosurgery should not be offered to patients who are willing to keep their potency. There are few published data on the effect of primary cryosurgery on quality of life. One study showed that the quality of life will generally return to the level before treatment by one year after cryosurgery [29].

Nerve-sparing and focal cryosurgery

The application of nerve-sparing cryosurgery can improve the functional outcome after treatment with better potency rates. It is known, from incidental autopsy studies that up to 20–30% of prostate cancers are solitary and unilateral [30]. The use of saturation prostate biopsies (up to 24 cores) could delineate monofocal compared to multifocal prostate cancer. In a recent report radical prostatectomy specimens from patients with clinically localized prostate cancer were analyzed

[31]. Completely unilateral cancers were identified in 18% of patients and the majority of these tumours (72%) were low volume. In this study it was suggested that only a select group of men would be amenable to focal cryosurgery targeting one lobe. The feasibility of nerve-sparing cryosurgery by active warming of the neurovascular bundle (NVB) was evaluated in a canine model [32]. In this model NVB preservation was possible but not consistently reproducible. In some cases NVB preservation with active warming may result in incomplete peripheral prostate tissue ablation. The authors conclude that these results have significant clinical meaning when attempting nerve-sparing cryosurgery. Because of the possible compromising effect on oncological outcome, nerve-sparing focal therapy should be considered experimental. In a preliminary study 9 patients were treated with focal, unilateral nerve-sparing cryosurgery [33]. After a mean follow-up of 36 months, all patients had a stable PSA and negative biopsies. Seven patients remained potent. The authors have appreciated the problem of multifocality in many prostate cancers and advised the patients to undergo repeated biopsies at a stable PSA level. Lambert et al. [34] reported the safety and efficacy of focal cryosurgery to preserve genitourinary function in men with localized, unifocal disease. With a median follow-up of 28 months, 84% were without biochemical failure and 68% remained potent. No patient had worsened LUTS, incontinence, rectal pain, perineal discomfort or fistula formation. Based on a 3-year observation period, focal cryosurgery of the prostate appeared to be associated with minimal morbidity and a promising efficacy.

Modern imaging techniques like 3-T endorectal coil MR imaging, dynamic contrast enhanced MRI and 3D MR spectroscopy have emerged with promising features in prostate cancer delineation [35,36]. Although these modalities are not widely available yet, an improvement in the detection of tumour volume and local extension as well as precise image-guided prostate biopsies is possible. Further, the results of focal therapy can be monitored with these techniques. Other innovations like real-time 'cellular' imaging [37] and computer planned positioning of the probes will improve efficacy and safety of the treatment.

Salvage cryosurgery of the prostate

In the EAU guidelines 2007 it is stated that achieving a PSA nadir after radiotherapy

of less than 0.5 ng/ml seems to be associated with a favourable outcome. The interval before reaching the nadir PSA may take up to 3 years or more. A PSA rising more than 2 ng/ml above the nadir PSA is the current definition of biochemical failure after radiotherapy. Also, the PSA doubling time following radiotherapy appears to aid in predicting the time to prostate cancer-specific death. Local recurrence rates after curative radiotherapy, confirmed by prostate biopsy, vary between 25% and 30% [38-41] and even a percentage of over 90% has been reported [42]. Recently, Touma et al. [43] reviewed the published data of salvage therapies following radiation failure. The authors state that the final success rate of curative radiotherapy depends on the modality being used, like conventional radiotherapy, 3DCRT or intensity modulated conformal radiotherapy (IMRT). It has been proven that dose escalation is an independent predictive factor of outcome. Also, local failure was found to be a strong predictor of distant metastasis. Others have suggested that recurrent prostate cancers are biologically more aggressive, either because of cytological evolution, perhaps induced by radiation or due to the progression of an innately aggressive tumour already resistant to radiation [44]. Therefore, in a patient with low risk of systemic disease (pre-treatment tumour stage, negative restaging imaging and greater than 12 months' PSA doubling time) and a life expectancy of more than 10 years salvage cryosurgery may be applied when PSA reaches 2 ng/ml above nadir after an interval from radiotherapy of at least 18 months.

Because of the relatively high rates of local disease recurrence after radiotherapy and its implications for outcome, salvage treatment options with curative intent have been applied since 1985 when the first series of salvage radical prostatectomy was published [45]. Five-year bDFS rates after salvage radical prostatectomy have been reported varying from 55% to 69% [43].

Clinical outcome

Biochemical failure rates of salvage cryosurgery also depend on the PSA threshold being used. Again, like for primary cryosurgery, there is no clear definition of failure. In an older series of salvage cryosurgery Pisters et al. [4] reported on 150 patients comparing a single and a double freeze-thaw cycle for local recurrence after radiotherapy. The mean follow-up was 13.5 months and the PSA threshold

Table 3 Results of salvage cryosurgery

Ref. (with actuarial data)	No. patients	Median follow-up in months (range)	Technique	PSA threshold	Low risk	b DFS (%) Intermediate risk	High risk [a]	nADT (%)	Duplication data [b]: y/n (reference)
de la Taille et al. [54] (1-year data)	43	22 (mean) (1-54)	LN/Ar	< 0.1	66 (all risk groups)			100	y (57)
Chin et al. [48] (5-year data)	118	19 (3-54)	Ar	< 0.5	NA	NA	34	60	y (58)
Ghafar et al. [57] (2-year data)	38	21 (mean) (3-37)	Ar	Nadir + 0.3	74 (all risk groups)			100	y (54)
Han et al. [11] (1-year data)	18	12 (NA)	Ar	< 0.4	77 (all risk groups)			NA	n
Bahn et al. [69] (7-year data)	59	82 (NA)	Ar	< 0.5	59 (all risk groups)			NA	y (47)
Creswell et al. [14] (1-year data)	20	9 (1.5-18)	Ar	< 0.5	67 (all risk groups)			NA	n
Ismail et al. [13] (5-year data)	100	33 (mean) (12-79)	Ar	< 0.5 ASTRO	73 59 (all risk groups)	45	11	46	n
Ng et al. [58] (8-year data)	187	39 (mean) (NA)	Ar	Houston	56	NA	14	71	y (48)
Pisters et al. [47] (5-year data)	279	22 (SD ± 25)	LN/Ar	ASTRO Phoenix	59 (all risk groups) 55 (all risk groups)			NA	y (69)

a) d'Amico risk stratification (1992 American Joint Committee on Cancer): low risk = PSA < 10 ng/ml and Gleason biopsy ≤ 6 and clinical stage T1c-T2a; intermediate risk = PSA 10-20 ng/ml or Gleason biopsy 7 or clinical stage T2b; high risk = PSA > 20 ng/ml or Gleason biopsy ≥ 8 or clinical stage ≥ T2c; nADT, neoadjuvant androgen deprivation therapy.
b) Duplication of reporting some patient data likely: yes or no (reference).
NA, not available; SD, standard deviation; LN, liquid nitrogen; Ar, argon gas; bDFS, biochemical disease free survival; ASTRO = three successive rises in PSA; Houston/Phoenix = PSA 2 ng/ml above nadir.

was < 0.1 ng/ml. Six months after a double freeze-thaw cycle, a higher negative biopsy rate was found of 93% compared to 71% after a single freeze-thaw cycle. The biochemical response rate after a double freeze was favourable with a bDFS of 56%. Data from Allegheny General Hospital, Pittsburgh, USA, with different cryosurgery techniques being used, demonstrate a 10-year bDFS of 57%. The PSA nadir level was < 0.4 ng/ml and failure was defined as two consecutive rises in PSA level of 50% or more [46]. Data from the largest database on salvage cryosurgery (COLD Registry) [47], in which 14 physicians participated and 277 patients were treated with either liquid nitrogen or gas-based technology, the five-year actuarial bDFS was 59% according to the ASTRO definition of biochemical failure. Again, the results of this database are assembled from many centers which leads to overlap of reporting. The results of the latest series of third-generation salvage cryosurgery are comparable to or even better than the previous techniques (Table 3). Several authors have defined predisposing factors for a worse outcome of salvage cryosurgery, including high PSA > 10 ng/ml and high Gleason score > 8 [48-50]. Also, patients with clinical stage T3 or T4 disease have an unfavourable outcome [48,49]. Complete ablation of the prostate is usually not attained in salvage cryosurgery, subsequently resulting in the release of PSA. In two series of salvage cryosurgery viable benign prostate tissue was identified in a substantial number of prostates, even though the biopsies after cryosurgery were negative for cancer [51,52]. This suggests incomplete ablation of the prostate was performed, but recurrence rates after salvage cryosurgery were not associated with this presence of benign prostate tissue [52].

Complication rates

Salvage radical prostatectomy is technically more challenging than primary prostatectomy. Significant complications will occur because of tissue plane obliteration, fibrosis and radiation-induced vasculitis. The average rates of rectal injury, anastomotic stricture and urinary incontinence are 6.6%, 18% and 45%, respectively [43]. Therefore, cryosurgery has emerged as a feasible minimal invasive treatment, although the complication rates are higher than those of primary cryosurgery (Table 4). This is especially true for incontinence rates and pelvic pain [53,54]. Initial salvage cryosurgery series reported incontinence rates of 73% or higher [4,55]. With third-generation techniques a significant decrease in serious

Table 4 Complications (%) after salvage cryosurgery

Ref.	No. Patients	Tech-nique	Fistula	Slough	Reten-tion	Inconti-nence	Impo-tence	UTI	Peri-neal pain
de la Taille et al. [54]	43	LN/Ar	0	0	4	9	NA	9	26
Chin et al. [48]	118	Ar	3.3	5.1	8.5	6.7	NA	NA	NA
Ghafar et al. [57]	38	Ar	0	0	0	7.9	NA	2.6	39.5
Han et al. [11]	18	Ar	0	11	0	11	86	NA	5.6
Bahn et al. [69]	59	Ar	3.4	NA	NA	8	NA	NA	NA
Ismail et al. [13]	100	Ar	1	2	2	13	86	NA	4
Ng et al. [58]	187	Ar	2	NA	21	3	NA	10	14
Pisters et al. [47]	279	LN/Ar	1.2	3.2	NA	4.4	NA	NA	NA

UTI, urinary tract infection; NA, not available; LN, liquid nitrogen; Ar, argon gas.

side effects, such as incontinence and rectourethral fistulas, was found [46,56,57]. Currently, the average incontinence rate is 8% (range 3%–13%), depending on the definition of incontinence. Mostly, incontinence is defined as the daily use of one or more pads [54]. In the COLD Registry database [47] a rectourethral fistula rate of 1.2% and incontinence rate of 3.8% was reported. The incidence of other complications, like urethral sloughing and strictures vary from 10%–15% to as low as 0%–5%, with the application of a urethral warming catheter and the newer cryotechnology [48,54,57]. Less frequently reported complications, but nevertheless bothersome are lower urinary tract symptoms (LUTS), occurring in up to 16% of patients [13,57,58]. The rates of impotence after salvage cryosurgery are high but many patients already have significant erectile dysfunction as a consequence of the foregoing radiotherapy. Perrotte et al. [59] found that quality of life was adversely affected especially by perineal pain, not so much by incontinence or impotence. They showed that treatment without an effective urethral warming catheter was highly associated with incontinence, perineal pain and slough. They concluded that salvage cryosurgery does not seem to have any

advantage compared to salvage prostatectomy in terms of morbidity and quality of life. Another study, in which quality of life was prospectively evaluated two years after salvage cryosurgery, showed that QOL returned to preoperative levels in all domains by 24 months after treatment, with the exception of urinary- and sexual functioning [60]. The overall QOL score was high and the satisfaction rates competed with the alternative of radical prostatectomy or androgen deprivation therapy. A single institution study, comparing quality of life between primary and salvage cryosurgery showed better physical and social functioning of the primary cryosurgery patients [61]. Overall QOL scores were high and the symptom scale pain scores were low for both treatment groups.

Evaluation

Despite the encouraging results urologists should be cautious when counseling patients about the outcomes of cryosurgery for a number of reasons. First of all, in many study protocols different cryosurgery systems have been used making comparison of outcome difficult. Because a uniform definition of treatment success is lacking, the end-points vary considerably. Usually varying definitions of biochemical recurrence are used as surrogate endpoints. Concomitant androgen deprivation therapy has an influence on short-term treatment results and must be taken into consideration (Tables 1 and 3). Most studies report the results of retrospective, single-institute case series and only one peer-reviewed publication of a randomized trial comparing cryosurgery with radiotherapy is available. Moreover, long-term follow-up data on disease-specific and overall survival are not available yet. Only one report of long-term bDFS with a median follow-up of 12.55 years has been published with a 10-year negative biopsy rate of 77% [62]. Furthermore, it should be realized that many studies are from only a few leading centers of excellence in the USA and Canada with considerable overlap in reporting of patient data (Tables 1 and 3). This typically leads to publication bias of positive studies and the results should be interpreted with caution. According to a recent Cochrane analysis, it must be concluded that results of cryosurgery are of low-level evidence [63]. Cryosurgery is a technically demanding procedure and the learning curve to reach an acceptable expertise level has been 200 cases

in earlier days [64]. Since then, new computer planning programs and guidance systems have greatly facilitated the procedure, but cryosurgery should be done only after adequate training.

Conclusions

There are increasing numbers of European centers applying cryosurgery for prostate cancer. The long learning curve has declined with new computer planning programs and guidance systems which greatly facilitate the procedure. Modern cryotechnology is therefore highly reliable and results are promising. The introduction of gas-based third-generation cryosurgery has decreased the complication rates significantly with similar clinical outcome when compared to older techniques. Salvage cryosurgery has more adverse effects, but remains an option for radiorecurrent prostate cancer patients. Stratifying patients into risk groups is an important aid for the urologist to select patients for cryosurgery. Further, a specific definition of treatment success is urgently needed. New developments like focal- and nerve-sparing cryosurgery for unifocal prostate cancer aim at further reducing the side effects but are still considered experimental. In counselling patients it is important to discuss the possible therapeutic gain of cryosurgery, the associated side effects and the impact on quality of life. The current data are derived from studies of low level evidence and this should be taken into consideration when making treatment decisions. Although biochemical disease free survival rates seem to be comparable to those of other treatment modalities, randomized trials with long-term follow-up are needed to define the role of cryosurgery in the treatment of localized prostate cancer.

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Chapter

06

Neoadjuvant and intermittent hormonal therapy

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Chapter 6
Neoadjuvant and intermittent hormonal therapy for prostate cancer

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Based on 'Handboek Prostaataandoeningen' (Uitgeverij De Tijdstroom, Utrecht, 2009); chapter 17.12: p. 425-8, and chapter 18.2: p. 493-5.

6.1 Neoadjuvant hormonal therapy

Introduction

The standard options for curative treatment of localized prostate cancer are radical prostatectomy and external beam radiotherapy (EBRT). In general, with these treatment options the local control is adequate. After radical prostatectomy an average 27%–53% of patients will have a biochemical recurrence within 10 years (rising prostate specific antigen (PSA)). The outcome is significantly worse for patients with T3 disease, high Gleason score ≥ 7 and lymph node metastases [1]. A biochemical recurrence after EBRT is seen in 30% of patients within 4 years [2]. Local tumor control is worse in locally advanced disease with subsequently more distant metastases as a result. These patients will benefit from additional treatment, for instance neoadjuvant androgen deprivation therapy (ADT).

Neoadjuvant ADT consists of treatment with a luteinizing-hormone releasing hormone (LHRH) agonist, an anti-androgen or a combination of LHRH agonists and anti-androgens (maximal androgen blockade). The prostate volume and tumor volume are reduced by neoadjuvant ADT. After the reduction of tumor volume less radiation dose is required for complete tumor destruction. The area of irradiated tissue is smaller which possibly leads to a reduction of radiation damage to the bladder and rectal tissues [3]. A synergistic effect of neoadjuvant ADT and radiotherapy has been described. An increase of the sensitivity to radiation is accomplished by reducing the hypoxic fraction of the tumor with ADT. In several in vitro- and in vivo studies this effect was shown [4]. By these means a better local control is achieved with combined EBRT. Further, apoptosis of micrometastases

can be induced by hormonal treatment. The ultimate goal of therapy is of course a survival benefit. The duration of neoadjuvant ADT remains a matter of debate, but for maximal volume reduction 8 months of ADT may be necessary [5]. Most of the literature on this subject is based on conventional radiation techniques. The complication rate has decreased significantly with modern techniques, such as 3D-conformation radiotherapy and intensity-modulated radiation therapy (IMRT) [6]. With these conformality techniques a precise radiation of the target volume is achieved with a higher dose than the conventional radiation techniques (up to 81 Gy). Therefore, a better local control is expected with sparing of surrounding tissues of bladder and rectum. No long-term results are known for these techniques. The role of neoadjuvant ADT with IMRT technique has not been extensively studied.

Oncological outcome

The oncological results of neoadjuvant ADT combined with EBRT have been described in several prominent articles [7-9]. The duration of neoadjuvant ADT in these studies varied between 3 to 8 months, and the patients mainly had locally advanced prostate cancer. In the RTOG 86–10 trial with 8 years of follow-up, patients with bulky tumors were treated with 2 months neoadjuvant ADT and 2 months of hormones concomitant with radiation therapy [7]. A significant improvement of local tumor control, disease-free and disease-specific survival were seen. For a subgroup of patients with Gleason 2–6, the overall survival improved as well (70% vs. 52%, $P = 0.015$). Surprisingly, patients with Gleason 7–10 showed no improvement of local control or survival. This finding seems in contradiction with the outcomes of other studies on the subject. However, the patients with Gleason scores 2–6 had an advanced clinical stage and high PSA, making them more or less high-risk patients with a considerable risk for metastases. A significant advantage for local tumor control, disease-specific and disease-free survival, after 6 months of neoadjuvant ADT, was shown by Denham et al. in the Trans-Tasman Radiation Oncology Group study [8]. All patients in this study had high-risk prostate cancer (Gleason score ≥ 8, PSA > 20 ng/ml, T3-T4). Laverdière et al. [9] showed an improved disease-free survival after 3 months of neoadjuvant ADT. Patients with localized prostate carcinoma (cT2) were included in that study as well.

Neoadjuvant ADT has been studied before radical prostatectomy as well and the goals are better local control, less positive surgical margins and downstaging in case of a locally advanced tumor. In a Cochrane review and meta-analysis, neoadjuvant ADT did not improve overall survival [10]. However, there was a significant reduction in positive surgical margin rates and significant improvement in other pathological variables such as lymph node involvement, pathological staging and organ confined rates. Follow-up was 7 years and patients were mainly treated with maximal androgen blockade. The use of longer duration of neoadjuvant hormones, that is either 6 or 8 months prior to prostatectomy, was associated with a significant reduction in positive surgical margins.

Duration of treatment

The debate on the sequence of hormonal therapy and EBRT continues, but also on the duration of neoadjuvant ADT. In a Canadian study, neoadjuvant ADT for 3 months was compared with 8 months [11]. A trend was seen for improved disease-free survival after 8 months for high-risk patients, but numbers were not statistically significant. As said before, in the Denham study a better disease-specific survival was shown for high-risk patients with 6 months versus 3 months of neoadjuvant ADT.

Summary

The role of neoadjuvant ADT combined with EBRT or before surgery has often been discussed in the literature. A better local control, disease-specific and disease-free survival is achieved with neoadjuvant ADT and EBRT, even for high-risk patients. A gain in overall survival may be possible, but needs confirmation in studies with longer follow-up. Therefore, neoadjuvant ADT before EBRT is often beneficial. The necessary duration of neoadjuvant ADT remains a matter of debate and seems to lie in between 3–6 months. The role of neoadjuvant ADT before surgery is limited. A better local control can be achieved but no improvement of survival is apparent.

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6.2 Intermittent hormonal therapy

Introduction

Androgen deprivation therapy (ADT) has become the standard treatment for advanced and metastatic prostate cancer, and can be achieved with surgical or chemical castration. With chemical castration, medication is used that is either blocking the testosterone synthesis (luteinizing-hormone releasing hormone (LHRH) agonists) or the peripheral mechanism of testosterone (steroidal or non-steroidal antiandrogens). When these medications are combined it is referred to as maximal androgen blockade (MAB). A good response and a normalization of prostate specific antigen (PSA) are seen in about 60%–80% of patients. Cell proliferation is inhibited by ADT and apoptosis occurs. Some of the stem cells survive ADT and proliferate into androgen-independent cells [1]. This process may already occur soon after the start of ADT. After a mean of 24 months prostate carcinoma becomes androgen-independent or, so called, castrate-resistant and the disease will progress. Theoretically, when ADT is stopped temporarily growth of androgen-dependent stem cells only may be initiated. The stem cells might remain hormone-sensitive in the next cycles of ADT. This is the basis of intermittent hormonal therapy. The development of androgen-independent tumors may therefore be delayed by intermittent hormonal therapy. Another claimed advantage of intermittent hormonal therapy is the preservation of quality of life (QOL) by a reduction in side effects that characterize ADT (loss of libido, erectile dysfunction, fatigue, loss of muscle mass, anemia, and osteoporosis). An obvious advantage of intermittent therapy is cost reduction by using less LHRH analogue depots. In the first study, in which the concept of intermittent therapy

was applied in the clinical setting, using diethylstilbestrol (DES) or flutamide, in 9 out of 10 patients with erectile dysfunction after ADT, a return of sexual function was seen during intermittent hormonal therapy [2]. Potency recovered at a mean of 3 months after stopping ADT. In several phase II clinical studies, a recovery of sexual functions and better QOL was shown once ADT was seized [3,4]. In most studies on intermittent hormonal therapy, ADT was stopped after PSA decline to the nadir (lowest value). Restart of ADT was initiated with a predefined PSA rise or with clinical progression. During this regimen, many patients have been off-therapy for several months.

Oncological outcome and toxicity

Phase II studies have shown the feasibility of intermittent hormonal therapy for recurrent prostate cancer after curative treatment and for metastatic disease. Both PSA response and clinical improvement were comparable to continuous ADT. Only few prospective randomized studies were performed to analyze the time to progression and survival. In the SWOG 9346 study, 1134 men with metastatic prostate cancer were randomized for intermittent- or continuous ADT, after 7 months induction course and PSA < 4 ng/ml [5]. No survival difference was seen between both groups. The PSA decline appeared to be a strong prognostic factor. Survival of patients with PSA < 0.2 ng/ml, < 4 ng/ml, and > 4 ng/ml was 75 months, 44 months, and 13 months, respectively. In a multicenter prospective randomized open-label study, with a follow-up of 30.8 months, 68 patients were included [6]. Patients were randomized between intermittent or continuous ADT, after 3–6 months of MAB induction course and a PSA £ 4 ng/ml on two separate occasions. The median duration of treatment cycles (maximal 6 months of MAB plus the off-therapy period) was 9 months, and 54% of the patients had ≥ 3 cycles. The median percentage of patients being off-therapy during study was 59.5%. The median 3-years progression rate for intermittent and continuous ADT was 7%, and 38.9%, respectively. The duration of the off-therapy period decreased in a linear way in subsequent cycles. Time to progression for intermittent and continuous ADT was 28 months versus 20.6 months. In another cohort study of 75 patients, intermittent therapy was started after 9 months of induction ADT treatment, and

a PSA < 4 ng/ml or a PSA decline ≥ 90% compared with the pre-treatment PSA value [7]. With a PSA rise > 20 ng/ml another cycle of 9-months ADT was started. Median survival was 95 months for patients with localized or locally advanced prostate carcinoma, and 87 months for patients with metastatic prostate cancer. Castrate-resistant tumors developed earlier in patients with metastatic prostate cancer. The 5-year survival rate for patients on intermittent therapy with locally advanced and metastatic prostate carcinoma was 100%, and 70%, respectively. Therefore, intermittent hormonal therapy is shown to be feasible in patients with advanced prostate cancer and progression-free survival is at least comparable to continuous ADT.

The characteristics of intermittent treatment with off-therapy periods seems beneficial to the patient. Costs are reduced and sexual functions improved, and QOL may be better. No data exist about long-term advantages of intermittent therapy for side effects like osteoporosis. The effects on long-term survival (> 10 years) have not been published yet. When future research will confirm an equal survival to continuous ADT with intermittent therapy, a better QOL and lower costs this treatment could replace continuous ADT. Finally, the results of the National Cancer Institute of Canada - Clinical Trials Group have recently been presented at the 2011 American Society of Clinical Oncology conference [8]. This randomized study on the effect of intermittent hormonal therapy on survival, after radiotherapy-recurrent prostate cancer, showed fewer hot flushes, and longer time to castrate-resistance in the intermittent group. There were no differences in fractures, osteoporosis, or heart attacks. Although the overall survival rates were similar, men on intermittent therapy were more likely to die of prostate cancer but less likely to die of other diseases. The death rate from prostate cancer in men on continuous therapy was 14%, but in the intermittent group it was 17.3%, a 26% higher death rate from prostate cancer. At the same time, the death rate from other causes was 60% in men on continuous therapy vs. 52.3% in men on intermittent therapy. That difference amounted to a 14% higher death rate from other causes in the men getting continuous therapy. Therefore, men need to be carefully counseled about the overall outcome, the tradeoff of a lower incidence of adverse effects, and a delay in the development of hormone refractory disease, but a greater likelihood of dying from prostate cancer.

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Chapter

07

Neoadjuvant androgen deprivation for radiotherapy

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Ilse Spitters-Post • J. Alfred Witjes • Johannes H. Kaanders • Peter F. Mulders

Chapter 7
Neoadjuvant androgen deprivation for prostate volume reduction: the optimal duration in prostate cancer radiotherapy

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Abstract

Objectives: For locally advanced prostate cancer, the results of radiotherapy are improved by combination with androgen deprivation therapy. Volume reduction achieved with neoadjuvant hormonal treatment can facilitate dose escalation without increasing the toxicity. The optimal duration of hormonal treatment, however, is unknown. The endpoint of this study is the optimal duration of androgen deprivation for prostate volume reduction in a cohort of patients scheduled for external beam radiotherapy.

Patients and methods: Twenty patients scheduled for external beam radiotherapy with cT2-3No/xMo prostate cancer were treated with a luteinizing hormone releasing hormone agonist (busereline) and nonsteroidal anti-androgen (nilutamide) for 9 months consecutively. Repeated CT scan examination was performed 3-monthly to measure prostate volumes until the start of radiation therapy. The analysis of volume reduction was performed with the Wilcoxon signed ranks test.

Results: The baseline median prostate volume for the cohort of patients was 82 cc (95% CI: 61–104 cc) with a median volume reduction of 31% (95% CI: 26%–35%) ($P < 0.0001$) after 3 months of androgen deprivation. Between 3 and 6 months, a median volume reduction of 9% (95% CI: 4%–14%) ($P < 0.0001$) was observed. The effect was more pronounced in large prostates (> 60 cc) than in small prostates (≤ 60 cc). In the total cohort of patients no significant volume reduction occurred between 6 and 9 months of maximal androgen blockade (MAB).

Conclusions: In this study, we have shown that the most significant prostate volume reduction is achieved after 3 months of MAB with a maximum reduction after 6 months. Therefore, the optimal duration of neoadjuvant androgen deprivation to reduce prostate volume before prostate cancer radiotherapy is 6 months. In small prostates 3 months of hormonal treatment may be enough for maximal volume reduction.

Introduction

The outcome of external beam radiotherapy for patients with locally advanced and bulky prostatic tumors can be improved with the application of neoadjuvant androgen deprivation. In vitro models have shown a radiation-sensitizing effect of androgen deprivation therapy [1]. Joon et al. [2] reported a supra-additive apoptosis with combination therapy in an in vivo study using Dunning rat prostate tumors. Several clinical studies have proven a significant advantage for the combination of radiotherapy and androgen deprivation relative to radiotherapy alone for selected patients with prostate cancer. As a result, in a review by the M.D. Anderson Cancer Center in Houston, Texas [3] recommendations were made for the duration of hormonal therapy. The author's advice is to include 6 months of androgen deprivation beginning 2 months neoadjuvantly for intermediate risk patients (T2b or Gleason 7 or prostate specific antigen (PSA) > 10–20). For patients with locally advanced (≥ T3) or high-risk prostate cancer (Gleason 8–10 or PSA > 20), longer-term androgen deprivation is recommended (e.g., 28 months). Low-risk patients (T1c-T2a or ≤ Gleason ≤ 6 or PSA ≤ 10) should not routinely receive androgen deprivation except in the setting of very large prostate volumes to improve dosimetric parameters. For brachytherapy in prostates > 60 cc, it is also common practice to combine the treatment with neoadjuvant androgen deprivation therapy for reasons of 'downsizing' the prostate to make the procedure technically more feasible [4].

The frequently asked questions about hormonal pretreatment are whether the amount of volume reduction depends on the initial prostate volume and, subsequently for how long the androgen deprivation should be administered. Hypothetically, these data can assist both radiation oncologists and urologists in determining the treatment schedule of androgen deprivation and radiotherapy based on the individual characteristics of the prostate.

The endpoint of this study is the optimal duration of androgen deprivation for prostate volume reduction in a cohort of patients scheduled for external beam radiotherapy.

Patients and methods

From August 2001 to May 2003, 20 patients with histologically confirmed localized prostate cancer cT2-3No/xMo, who were scheduled for external beam radiotherapy, were included in this phase II clinical trial. The study protocol was approved by the medical ethics review committee of our institution. If patients were eligible for enrolment into the study protocol, an informed consent was obtained. The initial diagnostic work-up included a clinical staging with digital rectal examination and/or MRI of the prostate, a bone scan, and pelvic CT scan. Demographics and medical history were taken and a baseline blood sample for PSA, hepatic-, and renal functions was obtained prior to the start of hormones. Patients had not received hormonal treatment or chemotherapy for prostate cancer in the past. An invasive neoplasm other than nonmelanoma skin cancer during the previous 5 years, hepatic failure, and severe respiratory insufficiency were exclusion criteria.

All patients received MAB using a 3-monthly subcutaneous depot of 9.9 mg luteinizing hormone releasing hormone (LHRH) agonist (buserelin) together with an oral nonsteroidal anti-androgen (nilutamide) 300 mg daily for 4 weeks, and 150 mg daily thereafter. Nine months after the start of hormonal therapy and within the fifteenth week following the last LHRH depot administration radiotherapy was planned.

Repeated CT scans were scheduled every 3 months (Fig. 1). The patients were asked to empty the bladder and rectum and drink half a liter of fluid, one hour before every CT scan, to ensure a comparable amount of bladder and rectum filling during the investigations. The CT scan (AcQSim big-bore spiral CT scanner; Philips Medical Systems, Bothell, WA) was taken with 3 mm slice thickness from the upper part of the sacro-iliac joints down to the perineum (the first CT scan

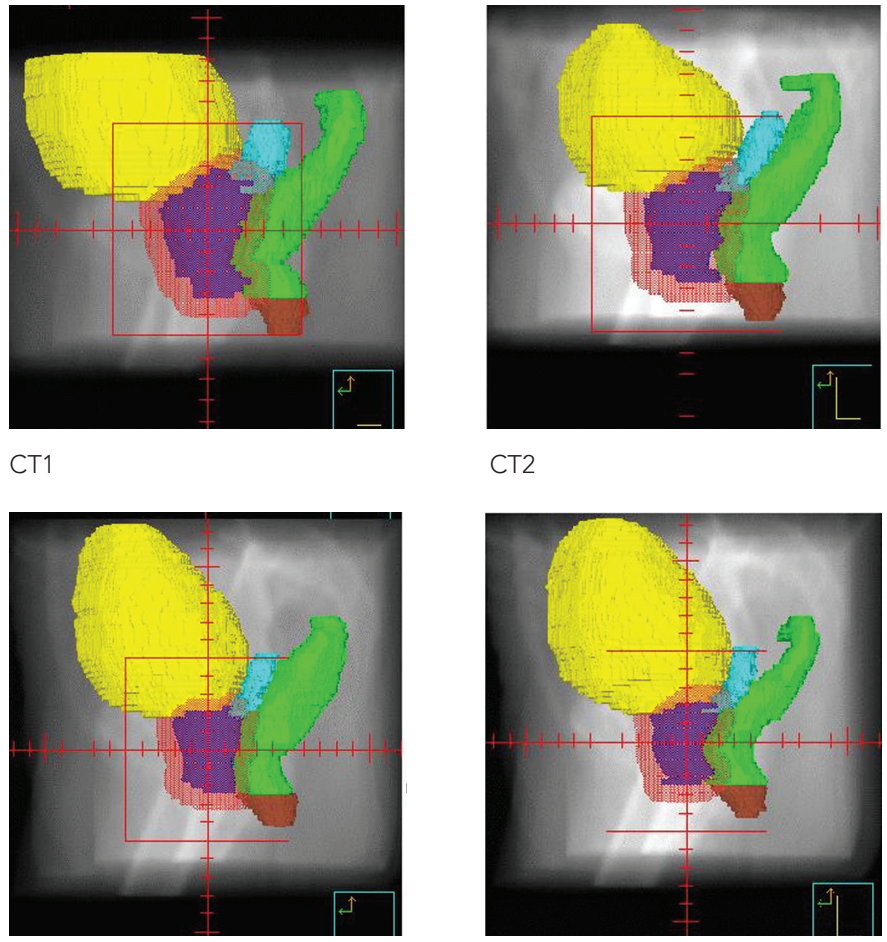

Figure 1

Prostate volume reduction (purple) shown on sagital plane of CT scans; CT1 = baseline; CT2 = after 3 months of MAB; CT3 = after 6 months of MAB; CT4 = after 9 months of MAB.

from lumbar vertebra IV). The baseline CT scan, which was made before the start of androgen deprivation therapy, was used for diagnostic purposes of the pelvic lymph nodes as well. Processing of the CT scan images encompassed manual

delineation of the prostate gland (excluding seminal vesicles) by a single observer (EvL), who was blinded for the duration of androgen deprivation, on all transverse slices where the prostate was visible and an automated volume measurement. On each CT scan the prostate was contoured using the Pinnacle³ radiation treatment planning system (Philips Medical Systems, Andover, MA). Prostate volumes were computed using the commonly applied voxel count method. Further, to evaluate if a certain volume of the prostate requires a specific duration of androgen deprivation, a comparison was made between small prostates of ≤ 60 cc and large prostates of > 60 cc. The CT scan at 9 months was ultimately used for the actual treatment planning of external beam radiotherapy.

Statistics

Statistical analysis was performed with SPSS for Windows version 9.0 (SPSS, Chicago, IL) or higher. A Wilcoxon signed ranks test was used to compare prostate volumes at specific time points during treatment. The null hypothesis was that prostate volumes would not change under influence of androgen deprivation therapy. A significance level of 0.05 was used to reject the null hypothesis. A Spearman correlation coefficient was calculated to evaluate if any linear correlation existed between numerical variables, namely PSA, Gleason score, the percentage of positive biopsies, and the relative volume reduction of the prostate after 3 and 6 months.

Results

Twenty-one patients were eligible for the study (Table 1). One patient died because of leukemia before the first CT scan evaluation and was excluded from the study. One patient died of cardiac arrest after 7 months of hormonal treatment. As a consequence, the prostate volume data of this patient were available until the CT scan evaluation at 6 months.

Fig. 2 shows the time trend of prostate volume reduction for the cohort of patients. The baseline median prostate volume was 82 cc (95% CI: 61 cc–104 cc). After 3 months of MAB a significant median volume reduction of 31% (95% CI: 26%–35%) ($P < 0.0001$) was achieved (Table 2). This volume reduction was seen in the subgroup of patients (n=15) with large prostates (> 60 cc) as well, with a median reduction of 31% (95% CI: 23%–37%) ($P < 0.0001$) (Table 3).

Table 1

Demographics of included patients (n=20).

Mean age (years)	71	(56-79)
T category		
T2	10	
T3	10	
Gleason		
≤ 6	13	
7	4	
8	3	
PSA (ng/ml)	12	(5-30)

When evaluating prostate volumes at 6 months compared with 3 months, a significant volume reduction of 9% (95% CI: 4%–14%) ($P < 0.0001$) was observed for the cohort of patients. For large prostates, the reduction was 10% (95% CI: 4%–18%) ($P < 0.001$). Between 6 and 9 months, there was no statistically significant reduction in prostate volume for the cohort of patients. In this study, every patient showed a reduction of prostate volume during the first 6 months of MAB.

Since the group of patients with prostates of ≤ 60 cc was small (n=5), no statistical analysis was performed. The volume reduction after 3 months of MAB was equal to the level that was achieved in large prostates (31%). After 3 to 6 months of MAB the volume reduction appeared less than in large prostates (8%).

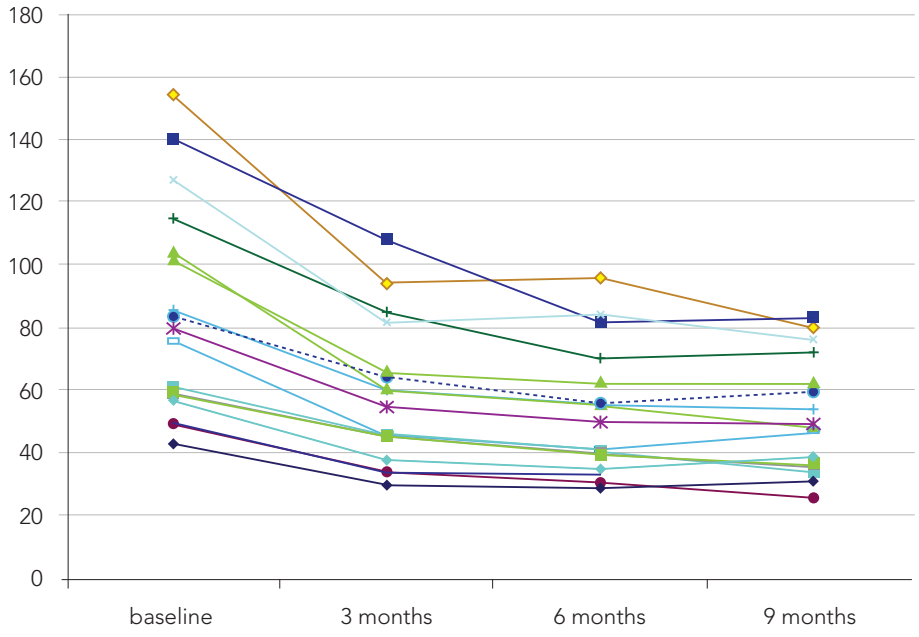

Figure 2

Graphic delineation of prostate volume reduction for study cohort during 9 months of MAB.

There was no correlation found between the PSA, Gleason score, the percentage of positive biopsies, and the relative volume reduction after 3 months and after 6 months.

Discussion

The synergistic effect of neoadjuvant androgen deprivation therapy and external beam radiotherapy can improve outcome in prostate cancer treatment. In an in vivo study, using Dunning rat prostate tumors, a supra-additive interaction of radiotherapy and androgen deprivation has been demonstrated [2]. This means

Table 2

Median prostate volumes during 9 months of MAB for the cohort of patients.

	Patients *(n)*	Median prostate volume (cc)	95% CI (cc)
Baseline	20	82	61 - 104
3 months	20	58	45 - 66
6 months	20	52	41 - 63
9 months	19	49	38 - 72

Table 3

Median prostate volumes during 9 months of MAB for patients with large prostates (> 60 cc).

	Patients *(n)*	Median prostate volume (cc)	95% CI (cc)
Baseline	15	86	79 - 127
3 months	15	65	50 - 85
6 months	15	56	41 - 82
9 months	15	54	46 - 76

that the effect on tumor cell kill due to the combination of treatments was greater than would be expected from the addition of the effects of the individual components. Further, it was described that the effect was specific for the sequence of external beam radiotherapy and androgen deprivation. The effect was time limited with a declining interaction after a longer interval between castration and the start of radiotherapy. It is currently unknown to what extent this delay of the start of radiotherapy can negatively influence the oncologic outcome in the clinical situation.

In localized prostate cancer, the final success rates of curative radiotherapy are dependent on the modality being used, such as conventional radiotherapy [5,6], 3D conformal radiotherapy (3D-CRT) [7], or intensity modulated radiotherapy (IMRT) [8]. The latter two allow for dose escalation, which is of paramount significance for the success of external beam radiotherapy. Improved treatment outcome by dose escalation has previously been reported, especially for intermediate- and high-risk patients [9-14]. In a retrospective analysis from the RTOG an improved survival in patients with high-dose radiotherapy was suggested [15].

The increased radiation dose harbors the risk of increasing the toxicity. With 3D-CRT, dose escalation is feasible though without a significant increase of grade III-IV toxicity of normal tissues surrounding the target volume [16]. However, the role of dose-escalated 3D-CRT for men with locally advanced (T3–4) prostate cancers is uncertain. In these patients, the increase of the target dose seems important for an improved local control but, especially in bulky tumors, it may be associated with increased side effects on the normal tissues of rectal wall and bladder. The volume of normal tissue that is exposed to high dose levels of radiation is an important predictive factor of the development of late toxicity [17]. Therefore, new techniques were developed in 3D-CRT and IMRT such as intra-prostatic implantation of gold markers and the use of electronic portal imaging systems for daily prostate position verification and correction procedures to decrease the margins of the radiation field [18-20]. By these means, dose escalation can be applied for bulky tumors as well.

An additional measure to confine toxicity in dose-escalated radiotherapy is to reduce the prostate volume with neoadjuvant androgen deprivation therapy. A target volume reduction of 30%–50% with androgen deprivation therapy may enable sparing of the surrounding normal tissues [21-23]. Some have shown that 3 months of androgen deprivation can significantly reduce the rectal volume included in the target volume [21,23]. Others have described a clear volume reduction of the prostate of 40% after 6 months of androgen deprivation, whereas the mean rectal volume receiving high-dose radiation decreased only 20% [24]. Therefore, the exact impact of prostate volume reduction on rectal toxicity has still to be determined.

The optimal duration of androgen deprivation has been a matter of discussion, and LHRH agonists are usually given for 3 to 6 months prior to the start of radiation treatment. Lilleby et al. [25] reported that the maximal reduction of prostate volume is achieved after 9 months, although the most pronounced changes occurred during the first 3 months. They advocated an extended duration of neoadjuvant androgen deprivation of more than 6 months. In our study, we have confirmed that the most significant reduction of prostate volume occurs during the first 3 months of MAB. On the other hand, we have found a maximal prostate volume reduction after 6 months of MAB without a significant reduction beyond this period. For large prostates, this may justify an extended duration of MAB for 6 months. For small prostates, 3 months of MAB may in fact be enough for the achievement of maximal prostate volume reduction. Although some reports have shown patient groups with prostate sizes of > 60 cc as well the median pretreatment prostate volume in this study was large compared to most prior reported studies. Therefore, this group may not be representative for patients undergoing hormonal pre-treatment in general.

We found no correlation between PSA, tumor grade, the percentage of positive biopsies, and prostate volume reduction. The numbers in this report are small though and further study about the influence of tumor characteristics on volume reduction would be of interest.

The accuracy of CT scan for prostate delineation and volume measurement has been a matter of debate in the literature. CT derived prostate volumes are larger than MR derived volumes with an average ratio of 1.3 [26]. Therefore, the use of MRI for delineation of the prostate is recommended, but since CT-MRI matching is not routinely available in all institutes, CT scan is considered a good alternative [27]. One report has shown an overestimation of prostate volume measurement by CT scan compared to TRUS, although the discrepancy between CT assessed and TRUS assessed volumes decreased in large glands and was shown to be negligible in prostates > 40 cc [28]. Badiozamani et al. [29] found that CT scan did not overestimate prostate volume when compared to TRUS, even for prostates < 40 cc.

In prostate brachytherapy reports 7%–69% of men that are treated for prostate cancer receive androgen deprivation therapy in some form. The goal is to downsize the prostate to make the brachytherapy procedure technically more feasible, although no substantial effects on disease-free survival are apparent, and treatment-related morbidity may be increased. For patients who were scheduled for brachytherapy, a more prominent volume reduction for large prostates was shown in one report [30], which is in agreement with our findings. The effect on volume reduction was greater with MAB versus LHRH agonists alone. All our patients were treated with MAB and we can therefore neither confirm nor invalidate these findings.

Lee et al. [31] describe that it is important to note that approximately 10% of men will have no significant prostate volume reduction under androgen deprivation therapy. In our cohort of patients, we found a consistent volume reduction in all patients during the first 6 months of MAB.

As a result of hormonal pretreatment, a delay between the initial diagnosis and the definitive treatment of localized prostate cancer occurs. In general, a delay of 3 months is considered to be without any clinical relevance. In daily practice, delay periods of more than 3 months are not unusual due to operation waiting lists and staging procedures. Whether this delay influences the outcome of these most often slowly growing tumors is an essential question. In literature, there is no consistent evidence found of a significant effect of surgical treatment delay on biochemical disease recurrence [32,33]. One study has shown an increased risk of biochemical progression in men with a delay of more than 6 months until surgery [34]. A treatment delay of no more than 6 months is therefore advocated. Others have not found a negative influence of treatment delay even for patients with a high risk of recurrence [35,36]. In one report, a delay beyond 9 months before radiotherapy was started did not seem to influence outcome [37], although another study showed that even a treatment delay of 2.5 months for high-risk disease adversely affected PSA outcome [38]. In all these studies about the impact of treatment delay, patients with neoadjuvant androgen deprivation were excluded from the analysis. In our opinion, a delay of 6 months from the initial diagnosis until definitive therapy for localized prostate cancer should not significantly influence outcome, especially under neoadjuvant androgen deprivation therapy.

Conclusions

A supra-additive interaction between androgen deprivation therapy and radiotherapy has been established for prostate tumors. The treatment outcome for external beam radiotherapy of localized prostate cancer is improved with dose escalation. A means to prevent increased toxicity is to downsize the prostate with androgen deprivation therapy.

In this study, we have evaluated the reduction of prostate volumes in patients who were assigned to MAB during 9 months before receiving external beam radiotherapy. The prostate volume measurements were done by repeated CT scan evaluations at 3-monthly intervals up to 9 months of MAB. The results of this limited series show that the maximal reduction of prostate volume was achieved after 6 months. The total prostate volume reduction was more pronounced for the cohort of patients with large prostates (> 60 cc) than for the group with small prostates (≤ 60 cc). The patient numbers in this study are small though. Especially for patients with small prostates, this comes with limitations in making conclusions about the required duration of androgen deprivation therapy.

By determining baseline prostate volumes, both radiation oncologists and urologists may have a tool to compose an individual treatment plan, and to adjust the duration of neoadjuvant androgen deprivation therapy according to prostate size. Taking into consideration the delay of definitive local treatment, we propose neoadjuvant androgen deprivation therapy of 6 months before radiotherapy. In small prostates, 3 months of hormonal treatment may be enough for maximal volume reduction.

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Chapter

08

Continuous vs intermittent androgen deprivation therapy

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Chapter 8

Continuous vs. intermittent androgen deprivation therapy for metastatic prostate cancer

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Abstract

Objectives: To analyze the predictive value of PSA for progression and the role of testosterone for quality of life (QOL) in patients with androgen deprivation therapy (ADT) for metastatic prostate cancer.

Materials and Methods: PSA and testosterone data were used from a phase III trial randomizing patients without progression and PSA < 4 ng/ml (n=193), after 6 months induction course, between continuous (CAD) (n=96) and intermittent (IAD) (n=97) ADT. The 2-year risk of progression was calculated for baseline PSA, 'fast' and 'slow' PSA decline to < 4 ng/ml (60 days cut-off), PSA nadir, performance status and pain. Testosterone kinetics and QOL were also evaluated. Univariate Kaplan Meier survival analysis and log rank tests were used to compare the risk of progression.

Results: For progression analysis, 173 patients' data were available. The 2-year risk of progression for baseline PSA < 50 ng/ml, 50 to < 500 ng/ml, and ≥ 500 ng/ml was 25%, 55%, and 76% (P = 0.03) in CAD, and 38%, 64%, and 85% (P = 0.006) in IAD, respectively. The 2-year risk of progression for PSA nadir ≤ 0.2 ng/ml, and > 0.2 to 4 ng/ml in CAD was 31% and 70% (P < 0.001), respectively. In the IAD group, a similar trend was seen. Patients with PSA nadir ≤ 0.2 ng/ml, though had significantly higher 2-year risk of progression compared to CAD (53% vs. 31% (P = 0.03)), respectively. PSA decline showed no predictive value. Patients without pain had a significantly lower 2-year risk of progression in both groups. Without ADT testosterone remained at castrate level for 4 months. After the first and second IAD cycle 92% and 46%, respectively, had a normalized testosterone. No QOL difference was found, although more side effects occurred in CAD.

Conclusions: Metastatic prostate cancer patients with high baseline PSA, pain, and high PSA nadir have a poor prognosis with ADT. Patients with low PSA nadir do significantly worse with IAD compared with CAD. Low testosterone after ADT and incomplete testosterone recovery may explain similar QOL. Therefore, IAD is not a good treatment option for many metastatic prostate cancer patients.

Introduction

The standard treatment for metastatic prostate cancer is androgen deprivation therapy (ADT) with a symptomatic and/or objective response in approximately 80% of patients [1]. Because many patients are on ADT for several years, the toxicity plays an important role. The treatment is associated with several side effects, including hot flushes, loss of libido, erectile dysfunction, cognitive dysfunction, fatigue, depression, osteoporosis, gynaecomastia, anaemia, loss of muscle mass, and metabolic syndrome with an increased cardiovascular risk [2-4]. The concept of intermittent androgen deprivation therapy (IAD) has been developed in preclinical studies aiming at the delay of the castrate resistant state [5,6]. Another goal was the reduction of toxicity, during the off-treatment phase, and improvement of quality of life (QOL), which was shown for the first time in early clinical studies and was ascribed to the recovery of serum testosterone levels [7,8]. However, these results were preliminary and patient numbers were small. Indeed, the exact relation of changing testosterone levels during IAD and QOL has been discussed in few reports so far. The remaining question is whether it is possible to identify a subgroup of patients, based on certain disease characteristics, which could benefit from IAD. Since a recent study has shown that the PSA response on ADT is a strong predictor of survival [9], our hypothesis is that PSA may also facilitate to identify patients that are suitable for IAD.

The goals of this study are to analyze the predictive value of PSA levels for progression and the role of testosterone kinetics on QOL in patients with metastatic prostate cancer during continuous or intermittent hormonal treatment. Further, the influence of baseline performance status (PS) and pain on progression is assessed.

Patients and Methods

Study design

The data from the Therapy Upgrading Life in Prostate cancer (TULP) study are used for this analysis. The TULP study is a multicenter, open, randomized controlled trial in which 43 centers from 12 countries have participated. The study has been approved by an Independent Ethics Committee and the Institutional Review Boards of participating clinics. A written informed consent of each patient has been obtained. All patients who already had received hormonal treatment for prostate cancer or had a neoplasm other than non-melanoma skin cancer were excluded. Other exclusion criteria were hepatic or renal dysfunction and the use of medication interfering with the interpretation of therapy results. Previous radiation therapy or surgery of the prostate was allowed. The primary objective of the original study was to determine whether time to clinical progression during IAD is equivalent to time to clinical progression during continuous androgen deprivation (CAD) in metastatic prostate cancer patients. Secondary objectives were to determine QOL, side effects, and overall survival.

Patients were included between January 1998 and September 2001 and the median follow-up from randomization was 31 months (range 0.8 – 47 months). Eligible patients had histologically proven prostate cancer with positive lymph nodes or distant metastases (T2-4N1-3M0 or T2-4NxM1), an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and a general life-expectancy of at least 18 months. A total of 290 patients were enrolled and received the study medication.

Patients were treated for a 6-month induction course of maximal androgen blockade (MAB) consisting of busereline 6.6 mg (Suprefact), a 2-monthly subcutaneous depot, and oral nilutamide 300 mg (Anandron) (once a day for the first 4 weeks and 150 mg daily thereafter). At the end of the induction course, patients without clinical progression and a PSA level < 4 ng/ml (n=193) were centrally randomized between CAD (n=96) and IAD (n=97). Non-responding patients (n=97), who either failed to achieve or maintain PSA < 4 ng/ml during the induction course or had clinical progression, were excluded from the study

Table 1

EORTC criteria (1989) for clinical progression in prostate cancer

Progression
- Any lesion increases in size or any new lesion appears, regardless of what the response of the other lesions has been
- Increase in any measurable deposit by more than 25%
- Increase in volume of primary tumor by more than 50%
- Significant deterioration in symptoms, decrease in weight, or decrease in performance status
- Increase in acid or alkaline phosphatase alone is not to be considered an indication of progression

protocol and were not followed for survival. These patients were treated off-study according to the treating physician's choice. At the time of study design (mid-1990s), there was little experience with IAD. The rationale for randomizing patients who reached a PSA threshold < 4 ng/ml was empirical and based on preliminary reported data. Also, the moment of reinstitution of androgen deprivation during off-therapy intervals when a PSA rise ≥ 10 ng/ml (M0 disease at baseline) or ≥ 20 ng/ml (M1 disease at baseline) occurred, was chosen on the basis of available data. In patients randomized for IAD, the ADT was discontinued and reinstituted when PSA reached the aforementioned values. Each subsequent IAD cycle consisted of a variable period of MAB, until PSA level reached < 4 ng/ml again, and an off-treatment phase. In both randomization groups, MAB was administered continuously once clinical progression occurred. Patients were provided with medication during the study protocol, consisting of a maximum of three cycles of IAD. Clinical progression was assessed according to the European Organization for Research and Treatment of Cancer (EORTC) criteria used in the 1990s (Table 1) [10]. PS was scored at months 2, 4, 5, and 6, and 2-monthly after randomization. Clinical evaluation for tumor stage or progression was performed

at randomization and 6-monthly thereafter or as clinically indicated until the end of the study. Tumor dimension assessment was performed by digital rectal examination or transrectal ultrasonography and radiological evaluation by bone scan, chest X-ray, ultrasonography or computerized tomography of the abdomen. QOL assessment was done with the EORTC general health related quality of life questionnaire (EORTC QLQ-C30-version 2.0). Also a validated disease specific questionnaire (EORTC module for prostate cancer, QLQ-PR24) was used. Every six months, plus at month 8, patients filled out these questionnaires. Laboratory tests were performed 2-monthly at an independent central laboratory (Bio-Inova Life Sciences International, Plaisir, France) and contained a hematologic and chemistry profile, including PSA and testosterone values. The post-study analysis of PSA and testosterone values in 2010 has been performed by an independent biostatistician (B.S.) at Factum Statistics (Offenbach/Main, Germany).

Statistical analysis methods

The objective of this analysis is to determine if PSA values are predictive for progression in men treated with ADT and to identify patients that are suitable for IAD. The variables studied were dichotomized for analysis of clinically relevant thresholds: (1) baseline PSA value at enrolment; (2) PSA decline to < 4 ng/ml during the induction course, divided into 'fast' decline and 'slow' decline, with a cut-off of 60 days; and (3) PSA nadir value after the induction course to either ≤ 0.2 ng/ml or > 0.2–4 ng/ml. The influence of baseline PS and pain medication on progression rates was also evaluated. A 2-year risk of progression could be calculated from the follow-up data. Further, testosterone kinetics during ADT and the subsequent correlation with QOL during CAD and IAD were analyzed.

Cox proportional hazard regression analyses of time to clinical progression by randomization group showed that the proportional hazards assumption was not met based on visual inspection and scaled Schoenberg residuals. Parametric multivariate regression analysis subsequently showed no differences in incidence rate ratios comparing the two randomization groups with or without adjustments for pretreatment cancer type (distant metastasis: yes or no), pretreatment performance status (increase of 1 category on WHO scale), and pretreatment pain medication (increase of 1 category on pain scale). Therefore, we decided to use univariate Kaplan-Meier survival analysis and log rank tests to visualize and compare the risk of clinical progression for all predictive factor analyses. Differences between the 2 treatment groups were tested for statistical significance by calculating a log rank test or X^2 test. The analyses were performed with the Statistical Analysis System (SAS, Cary, NC) ver. 8.2 and the statistical software SPSS for Windows (release 15.0.0) SPSS Inc., Chicago, IL. No corrections or adjustments were made for missing data.

Results

Patients' characteristics

Patient demographics and medical history showed no differences between randomization groups, except for age [in the IAD (n=97) group 66.8 years (SE 0.8); in the CAD (n=96) group 69.1 years (SE 0.8)]. This difference was considered clinically irrelevant for the risk of progression, since age is not a known prognostic factor for efficacy during hormonal therapy. Tumor characteristics in the randomized patient groups were similar, except for the number of distant metastases with more multiple, mainly bone metastases in the CAD group (Table 2). The non-responder group (n=97) was excluded from further analysis. This non-responder group showed more T4 tumors compared with the randomization group (33% vs. 17%, respectively). Also, a worse baseline PS and more painful metastases were seen. Close accountability of study drug consumption during the hormonal therapy intervals confirmed the good compliance with treatment. Because of protocol violation in 5 patients, testosterone analyses could be performed for the remaining 188 patients. For the calculation of the predictive value for progression of PSA, 20 patients of the initial 193 were lost to follow-up (13 in the CAD group; 7 in the IAD group), leaving 173 patients for analysis.

PSA values

In Table 3, the 2-year risk of progression for all evaluated predictive factors is shown. Considering baseline PSA, a significant difference was seen in the 2-year risk of progression for higher PSA values in both the CAD group (Log rank: $P = 0.03$) and the IAD group ($P = 0.006$). The associated Kaplan-Meier curves are

Table 2

Tumor characteristics at enrolment.

	Not randomized group (n=97)	CAD (n=96)	IAD (n=97)	X^2 test *(P)*
Tumor stage				
T1		-	1	
T2	15	25	27	
T3	50	54	51	*P* = 0,79
T4	32	15	18	
Tx		2	0	
N0	40	44	39	
N1-3	36	38	38	*P* = 0,51
Nx	21	14	20	
M0	11	19	18	*P* = 0,97
M1	86	77	79	
Distant metastases				
Single	4	7	20	*P* = 0,013
Multiple	82	70	59	
Bone	85	74	71	
Visceral	6	1	3	*P* = 0,60
Missing	7	5	11	
Gleason				
2-4	9	13	13	
5-7	44	47	40	*P* = 0,60
8-10	43	35	41	
Gx	1	1	3	

(table 2, continued)

	Not randomized group (n=97)	CAD (n=96)	IAD (n=97)	X^2 test *(P)*
PSA				
Median (ng/ml)	NA	108 (11-8173)	98 (7-3006)	*P* = 0,58 *
Testosterone				
Median (ng/ml)	NA	4.0 (1.8 - 8.0)	4.1 (1.4 - 8.5)	*P* = 0,55 *
ECOG				
0	35	70	72	
1	42	19	19	*P* = 0,95
2	20	7	6	
Pain medication				
No analgesics	55	76	76	
Non-narcotic analgesics irregular use	17	9	10	
Non-narcotic analgesics regular use	11	7	6	*P* = 0,94
Narcotic analgesics irregular use	4	2	3	
Narcotic analgesics regular use	10	2	2	

T = tumor; N = lymph node metastases; M = distant metastases;

PSA = prostate specific antigen; ECOG = Eastern Cooperative Oncology Group;

NA = not available.

X^2 test for statistical analysis of differences between randomization groups (*P* value).

* Mann-Whitney U-test.

shown in Figure 1. To estimate the influence of PSA decline on clinical outcome, the 2-year risk of progression was calculated for the 'fast' and 'slow' decline groups in both randomization groups. No significant differences were seen per group. Concerning the CAD group, the predictive role of PSA nadir was evaluated, and a significantly lower 2-year risk of progression was seen for PSA nadir ≤ 0.2 ng/ml compared with PSA > 0.2–4 ng/ml (Log Rank: $P < 0.001$). For the IAD group a difference was seen, but numbers were not statistically significant ($P = 0.31$). Overall, patients with IAD showed a trend of higher progression rates compared to CAD, but the only significant difference was seen in patients with PSA nadir ≤ 0.2 ng/ml with a 2-year risk of progression of 53% vs. 31% ($P = 0.03$), respectively. Patients without pain medication at enrolment had a significantly lower 2-year risk of progression in both groups. Patients without physical impairments seemed to do clinically better than the impaired ones but differences were not statistically significant.

Testosterone kinetics

After 2 months of the induction course, the median testosterone value was 0.2 ng/ml in both randomization groups. All patients had reached castrate testosterone (< 0.5 ng/ml) levels within 4 months of MAB and the median time to reach the PSA nadir was 4 months. In the CAD group, the median serum testosterone remained stable at castrate level (0.2 ng/ml) during the complete study period. The median serum testosterone in the IAD group started to rise above 0.2 ng/ml at 10 months to normal levels at 12 months, i.e., 8 months after the last busereline injection. From 12 months onwards, testosterone levels were fluctuating, showing the nature of IAD. In every cycle, after reintroduction of ADT, the median time to reach the nadir testosterone level was consistently 2 months.

The mean duration of the first IAD cycle was 19 months, with an off-treatment interval of 13 months. During this interval, the mean duration of castrate testosterone level was 7 months, and patients had a normal testosterone for 6 months. The percentage time off-therapy decreased with successive cycles (Table 4). During the off-treatment intervals of cycles 2 and 3, the mean duration of castrate testosterone level was 4.7 months and 1.2 months, respectively. In the remaining time of these intervals, patients had a normal testosterone, but the

Table 3

Two-year risk of progression (percentage ± SE) for predictive factors.

Predictive factor	CAD (n=83)	IAD (n=90)	Log rank test (*P*)
PSA baseline			
< 50 ng/ml	25% (± 8.9)	38% (± 9.7)	*P = 0.41*
50 - < 500 ng/ml	55% (± 10.6)	64% (± 8.3)	*P = 0.82*
≥ 500 ng/ml	76% (± 18.0)	85% (± 13.1)	*P = 0.20*
	P = 0.03	*P = 0.006*	
PSA decline to < 4 ng/ml			
Fast	47% (± 10.4)	61% (± 9.8)	*P = 0.31*
Slow	47% (± 8.5)	57% (± 8.1)	*P = 0.62*
	P = 0.64	*P = 0.96*	
PSA nadir			
≤ 0.2 ng/ml	31% (± 8.3)	53% (± 7.6)	*P = 0.03*
> 0.2 – 4 ng/ml	70% (± 9.5)	68 % (± 10.6)	*P = 0.11*
	P < 0.001	*P = 0.31*	
Performance status			
No physical impairment	43% (± 8.6)	53% (± 6.9)	*P = 0.32*
Restricted	67% (± 12.2)	76% (± 11.6)	*P = 0.82*
	P = 0.11	*P = 0.12*	
Pain			
No analgesics	39% (± 8.0)	50% (± 6.8)	*P = 0.21*
Analgesics	79% (± 10.4)	80% (± 11)	*P = 0.97*
	P < 0.001	*P < 0.01*	

Fast decline PSA < 60 days; slow decline PSA ≥ 60 days. SE = standard error.

Log rank test for statistical analysis of differences between randomization groups (*P* value).

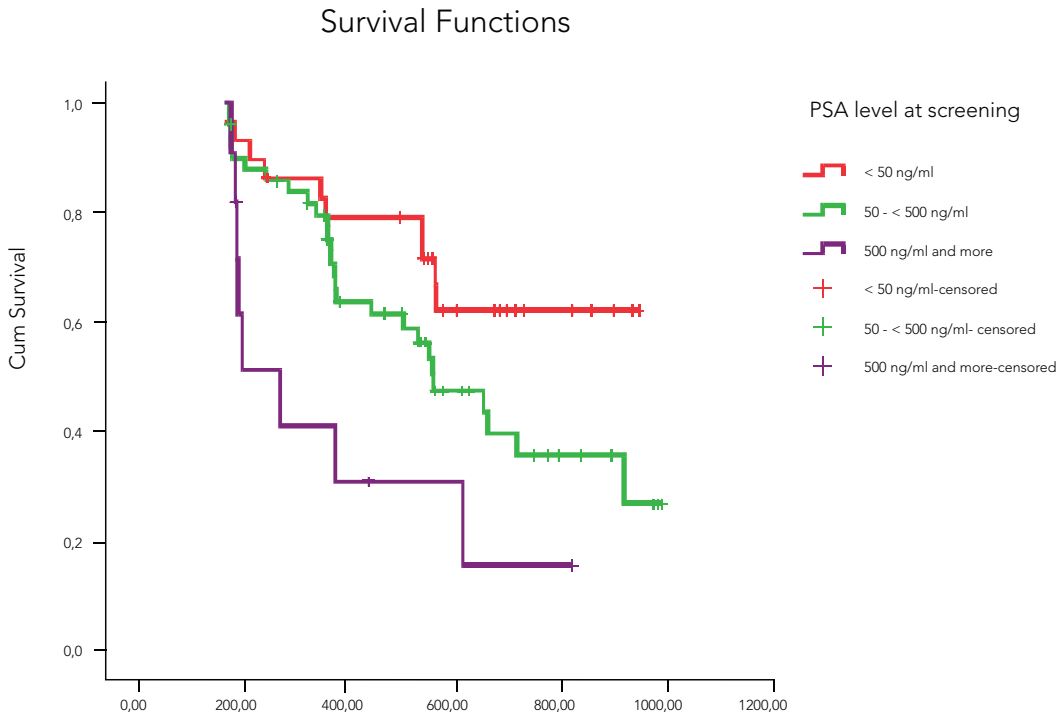

Figure 1a

Kaplan-Meier curves of clinical progression in IAD for different baseline PSA levels.

duration was negligible. When ADT was reintroduced, at the end of the first cycle, 92% of patients had a normalized serum testosterone. This means that 8% had castrate levels of testosterone and rising PSA. At the end of the second cycle, the number of patients with castrate testosterone levels and rising PSA was 46%.

QOL

Overall, there was no clinically significant difference in QOL scores between patients. Further, no consistently significant difference for any single QOL

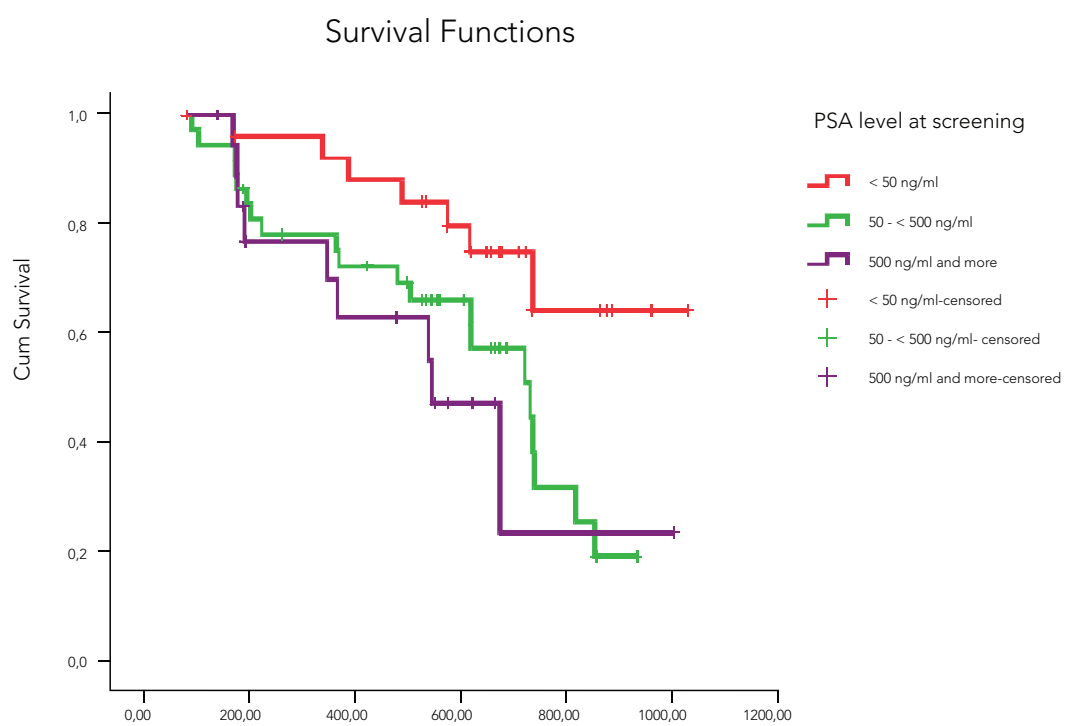

Figure 1b

Kaplan-Meier curves of clinical progression in CAD for different baseline PSA levels.

parameter was found between the treatment groups (data not shown). As required for valid analyses, across all patients, more than 70% of QOL scale scores were available, indicating a reliable QOL assessment. A large number of patients had one or more concurrent side effects during treatment (Table 5); 91 (95%) in the CAD group and 88 (91%) in the IAD group. Overall, a trend of more side effects like hot flushes, nausea, constipation, dyspnea, and depression was seen in CAD patients.

Table 4

Duration treatment intervals and testosterone levels during IAD.

	Cycle 1 (n=97)	Cycle 2 (n=51)	Cycle 3 (n=13)
Time on-therapy (months) Mean ± SD	6 ± 0.5	4,5 ± 2.9	3,8 ± 3
Time off-therapy (months) Mean ± SD	13 ± 6	5 ± 5	0,6 ± 1,2
Percentage time off-therapy (%) Mean ± SD	65 ± 14	40 ± 34	14 ± 24
Total cycle duration (months) Mean ± SD	19 ± 5.9	9,5 ± 4.9	4,5 ± 2.9
Castrate testosterone (< 0.5 ng/ml) during off-treatment interval (months) Mean ± SD	7 ± 2.8	4,7 ± 3.9	1,2 ± 1.5

SD = standard deviation.

Table 5

Side effects

	No. pts. (%)		
Events	CAD (n=96)	IAD (n=97)	X^2 test (*P*)
Hot flushes	57 (59)	49 (50)	*P* = 0,28
Visual disturbances	32 (33)	32 (33)	*P* = 0,92
Nausea	19 (20)	11 (11)	*P* = 0,15
Constipation	16 (17)	7 (7)	*P* = 0,07
Dyspnea	12 (12)	6 (6)	*P* = 0,20
Erectile dysfunction	10 (10)	9 (9)	*P* = 0,98
Depression	11(11)	6 (6)	*P* = 0,30
Liver enzyme increase	5 (5)	8 (8)	*P* = 0,58
Gynaecomastia	7 (7)	4 (4)	*P* = 0,52
Anaemia	5 (5)	4 (4)	*P* = 0,99
Alcohol intolerance	4 (4)	3 (3)	*P* = 0.99

X^2 test for statistical analysis of differences between randomization groups (*P* value).

Discussion

In this study, comparing intermittent to continuous ADT for metastatic prostate cancer, the predictive value of PSA for progression and the role of testosterone kinetics on QOL were assessed. It is shown that high baseline PSA, pain, and high PSA nadir, after a 6-month induction course, are strong predictors of progression with hormonal therapy. Therefore, in these patients research should focus on alternatives for hormonal treatment. Overall, the negative impact on the risk of progression for all predictive values was more outspoken in the IAD group.

Consistent with our results, Prapotnich et al. [11] showed in a cohort study that patients with initial bulky tumors, numerous lymph nodes or bone metastases, baseline PSA > 100 ng/ml, rapidly progressive PSA slope (> 5 ng/ml per month), or severe pain are poor candidates for IAD, because they frequently achieve only a partial or short-term response. In the Finnish multicenter study [12] for intermittent therapy, patients with high baseline PSA and alkaline phosphatase, T4 and poorly differentiated cancers, and metastatic disease with more than 5 skeletal hotspots showed inadequate initial PSA response to ADT and were not considered good candidates for IAD. These patients with initial bad response to ADT were excluded from our study, leading to a selection bias towards relatively good prognosis patients. Intermittent therapy may be more useful in early stage disease, i.e., localized or local recurrent disease as already discussed by Grossfeld and associates [13].

Using data from the Southwest Oncology Group Trial 9346, Hussain et al. [9] evaluated the absolute PSA value after 7 months of ADT and found that 69% of patients had a PSA < 4 ng/ml at the end of the induction course, which is similar to our findings (67%). The PSA nadir appeared to be a strong independent predictor of survival in metastatic prostate cancer, with a median survival of 13 months for patients with PSA of > 4 ng/ml, 44 months for PSA > 0.2 to ≤ 4 ng/ml, and 75 months for PSA ≤ 0.2 ng/ml. In our study, patients with PSA nadir ≤ 0.2 ng/ml showed lower progression rates than PSA nadir > 0.2 to 4 ng/ml. It also appeared that IAD patients with low PSA nadir had significantly higher 2-year risk of progression than CAD patients. Therefore, these patients do not seem to be

good candidates for IAD. To our knowledge, this finding has not been reported before and supports CAD treatment for good-responders on ADT induction.

Considering testosterone kinetics and QOL, two phase II studies on intermittent therapy have supported that testosterone levels normalize in many, but not all, patients when they are off-therapy [14,15]. After 6 months of luteinizing hormone-releasing hormone (LHRH) analogue treatment, 90% of patients had a normalization of testosterone level within 18 weeks [14]. A median 12.9 weeks was needed for recovery of testosterone above castrate level, and older patients needed more time for recovery. Tunn et al. [15] found a normalization of testosterone in 91% of patients at the end of the first treatment cycle, and less recovery of testosterone levels in subsequent cycles. These results are similar to our findings. In our series, a median 4 months was needed for testosterone to rise above castrate level after the induction course. After median 6 months, normal levels were reached. This relatively slow recovery of testosterone may be explained by high age and a prolonged release of the busereline implant. A testosterone suppression of minimal 6 months was already proven for a 3-month implant 9.45 mg [16].

The majority of phase II studies have shown that IAD regimens have promising toxicity profiles as a result of testosterone recovery eliminating the side effects of ADT. Early phase III results suggested a better toxicity profile and also QOL [17], particularly with respect to sexual function. Not all studies have demonstrated between-group differences for QOL [18]. A Cochrane review commented that IAD appears to be slightly better than CAD in terms of reducing the levels of erectile dysfunction [19]. In our study, a bias is seen in sexual function measurement as very few patients had erections at baseline, after previous surgery, or radiation therapy. No differences for QOL were seen at the time of first measurement (month 8). At the second measurement (month 12), although testosterone levels in IAD were rising, the median testosterone had still not fully recovered and there were no QOL differences. The next QOL measurement was performed at 18 months, when most patients had normal serum testosterone levels. Interestingly, even then, no significant difference in any QOL parameter was measured. The reason for this is unclear, but may be due to high age and better acceptance of side effects. In another study, evaluating the general health-related QOL of 250 patients treated with IAD,

a trend of progressive improvement paralleling testosterone recovery was shown [20]. However, the rate of recovery was slower than the rate of deterioration during ADT and the maximum recovery was seen only after 9–12 months. In general, by using the PSA limits that we used for re-starting of hormonal therapy, the recovery time for testosterone may be simply too short to detect an improvement in QOL. In successive cycles of our study, the off-therapy interval became shorter, leading to less recovery time for testosterone. Numbers of patients with a normalized testosterone at the end of each cycle therefore decreased.

In our study, the specific moment of side effects occurring was not analyzed but overall a trend of more side effects in CAD patients was seen. This favors intermittent therapy, although some of the toxicity like dyspnea and visual disturbances were specifically nilutamide-related and may be less prominent with other anti-androgens. These side effects, though, certainly affect QOL in an adverse way. It still remains unclear whether IAD can prevent long-term side effects of ADT and this needs further study. Another obvious advantage of IAD is economical, with our patients being off-therapy 40% of the time.

Our study has several limitations: Although only two large phase III trials with more than 500 patients were reported [9,18], this is a relatively small study with 193 randomized patients and consequently limited statistical power. The intermediate follow-up duration (31 months) makes an evaluation of cancer-specific survival impossible, as only a few patients had died and, therefore, clinical progression was chosen as the endpoint for the predictive value analysis. Clinical progression was measured with the EORTC criteria that were introduced in 1989 [10]. Most metastatic patients have disease limited to the bone, which is notoriously difficult to assess for response. Therefore, future trials should include other criteria for progression, including, for instance, time to PSA progression according to the Prostate Cancer Working Group criteria for castrate resistant prostate cancer [21]. One should realize that although the association of biochemical progression and overall survival in metastatic prostate cancer has been confirmed at the individual patient level during hormonal therapy, PSA as surrogate endpoint for overall survival could not be statistically validated in trials of hormonal treatment [22]. The analysis of PSA and testosterone was not part of the original study protocol, which

explains why these results are reported late. The progression data of 20 patients were lost to follow-up and although unfortunate, these numbers do not seem to influence the results. PSA and testosterone measurements, and QOL assessments were performed at fixed 2-monthly and 6-monthly intervals, respectively. This monitoring frequency interferes with a more detailed analysis of PSA decline during hormonal treatment and the assessment of the exact correlation of testosterone kinetics and QOL.

The empirical choice of reinstituting ADT based upon a static PSA number rather than PSA kinetics could bias towards undertreatment of more aggressive cancers, and this is limiting the study. On the basis of a meta-analysis of IAD [23], showing a longer survival in patients in whom treatment was re-started when PSA level reached 15 ng/ml than in whom it was allowed to rise higher, our criteria may also need adjustment on the expense of less time for testosterone recovery.

Conclusions

Metastatic prostate cancer patients with high baseline PSA, pain, and high PSA nadir, after a 6-month induction course, have a poor prognosis with hormonal therapy. Overall, in this study patients on IAD seem to do worse than CAD. Also, IAD patients with low PSA nadir had significantly higher progression rates than CAD. After the induction course, serum testosterone values remain at castrate level for 4 months and testosterone recovery during the off-treatment phase is incomplete. This may explain why no benefit for QOL was found for IAD, even though more side effects occurred during CAD. Therefore, IAD is not a good treatment option for many metastatic prostate cancer patients.

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Chapter

09

Summary
Samenvatting

Chapter 9 Summary

Prostate cancer is diagnosed in more than 9.000 men in the Netherlands each year. A shift is seen towards younger age and more cancers are treated at an early stage. Ultimately, this may improve cancer specific survival but currently this remains uncertain. A downside of aggressive treatment of the patient are the associated side effects, which should be considered when treatment is discussed. The aim of this thesis is to evaluate the developments in prostate cancer treatment that focus on improving complication rates without compromising the oncological outcome.

In **chapter 2** the development of high-precision radiotherapy with the aid of fiducial gold markers is described. Clinical trials have shown a dose-response relationship in radiotherapy for prostate cancer. However, dose escalation potentially increases toxicity of the surrounding tissues, e.g. bladder, rectum, and anal canal by the high-dose exposure. The prostate is a moving organ with a few millimeters displacement on a day-to-day basis. Together with the patient set-up variations this demands certain treatment margins around the gland for adequate coverage of the target organ. Intraprostatic gold markers have an excellent visibility on daily electronic portal images during radiotherapy. This enables precise verification and correction of the prostate position, and smaller treatment margins. In this study, the influence of gold markers on treatment volume and radiation doses to surrounding tissues was investigated. Three historical treatment margins were reconstructed to show the reduction of Planning Target Volume: PTV 10 mm (no markers), PTV 7 mm (markers), and PTV 7/5 mm (markers and online correction). With the planning computed tomography (CT) scan system the treatment volume and radiation doses were calculated. A significant PTV reduction of 27% was achieved with gold markers. Subsequently, mean radiation dose reductions of 17% (±4.5%) to the bladder, 19% (±4.7%) to the anal canal and 12% (±3%) to the rectal wall were seen. Although it seems reasonable to presume that gold markers have a favorable impact on late toxicity profiles, this needs further clinical studies.

As the procedure of gold marker implantation is invasive, it can only be justified if complication rates are low. Therefore, in **chapter 3** complication rate and risk factors of transrectally implanted gold markers are analyzed. In 209 consecutive men with localized prostate cancer, four fine gold markers were inserted under ultrasound guidance, and the side effects were analyzed with questionnaires. Thirteen men (6.2%) had a moderate complication, consisting of pain and fever that resolved with oral medication. In 1.9% of men, minor voiding complaints were observed. Other minor transient complications, such as hematuria more than 3 days, hematospermia, and rectal bleeding, occurred in 3.8%, 18.5%, and 9.1%, respectively. Complications were seen more often in patients with advanced tumor stage, younger age, and shorter duration of hormonal therapy. In conclusion, the transrectal gold marker implantation is safe and well tolerated.

A potential curative treatment option for a biochemical recurrence after radical prostatectomy is salvage radiotherapy of the prostate bed. Also, patients with positive surgical margins and high-risk disease benefit from adjuvant radiotherapy. For these specific patient groups, image-guided radiotherapy with gold markers in the prostate bed and electronic portal imaging has been introduced recently. No large series have been described yet and experience with the implantation procedure is therefore limited. In **chapter 4**, the technique and complication rate of post prostatectomy ultrasound-guided transrectal implantation of gold markers are described. In 77 consecutive men with a biochemical recurrence or positive surgical margins after radical prostatectomy, and high-risk prostate cancer, three fine gold markers were implanted in the prostate bed. The feasibility of marker implantation was analyzed and marker migration was recorded with imaging. For complication rate measurement, the patients filled out questionnaires. Minor complications were rectal bleeding for one day in ten patients (13%), and voiding complaints in one patient. Moderate complications, like rectal discomfort resolving spontaneously within 7 days (n=2), nausea for two days (n=1), abdominal discomfort (n=1), and pain requiring analgesics (n=4), were seen in 8 patients (10%). The mean VAS score during implantation was 3.7 on a scale of 1 to 10. Postoperative strictures, which were considered to be a surrogate for fibrosis in the operation field, did not cause significant more pain during implantation. Transrectal gold marker implantation in the prostate bed, as part of post prostatectomy radiotherapy, is therefore feasible and safe. Pain is slightly more prominent, especially in younger patients, than with intraprostatic gold markers and analgesics could be advocated. No risk factors were found for bleeding or pain.

In **chapter 5**, a literature review is given after a Pub med search for data on primary and salvage cryosurgery of the prostate. It appeared that the introduction of gas-based third-generation cryotechnology has decreased side effects significantly, with similar oncological results compared to older cryosurgery techniques. The occurrence of severe complications like rectourethral fistulas (< 1%) has almost been eradicated, but the rates of erectile dysfunction remain high (90%). With salvage cryosurgery more side effects can be expected with an average incontinence rate of 8%, and fistulas up to 3.4%. Nevertheless, this minimal invasive treatment remains an option for radiotherapy recurrent prostate cancer because salvage prostatectomy has a high complication rate. However, the current cryosurgery data in literature are of low-level evidence which should be discussed when counseling the patients. Focal cryosurgery is considered experimental, but is an interesting new development in cryosurgery to improve complication rates. The performance of randomized trials with long-term follow-up should be advocated to define the ultimate role of cryosurgery in the treatment of localized prostate cancer.

Chapter 6 offers a review on the role of androgen deprivation therapy (ADT) in the neoadjuvant and intermittent setting. This chapter is the introduction to the clinical studies that are discussed in chapters 7 and 8. For locally advanced prostate cancer and high-risk patients neoadjuvant hormonal therapy gives better local tumor control and disease-specific survival when it is combined with radiotherapy compared with radiotherapy alone. Therefore, it should be considered standard care for these patients. The necessary duration of hormonal pretreatment, however, is a matter of debate and lies in between 3–6 months. The role of neoadjuvant ADT before surgery is limited. In patients with advanced or metastatic prostate cancer intermittent hormonal therapy has been proven feasible. Progression-free survival seems comparable with patients on continuous ADT. The off-treatment intervals lead to a reduction of costs and an improvement of sexual function, and sometimes quality of life. The effect of intermittent therapy on long-term complications of hormones, for instance osteoporosis and metabolic syndrome, is unknown. **Chapter 7** deals with the optimal duration of neoadjuvant ADT for prostate volume reduction before radiotherapy. In very large prostates, ADT before radiotherapy can downsize the prostate for improvement of dosimetric parameters, and a reduction of radiation dose to surrounding tissues. Twenty

consecutive patients with cT2-3No/xMo prostate cancer, who were scheduled for radiotherapy, were treated with 9 months of neoadjuvant ADT. Repeated CT scan examinations for prostate volume measurement were performed 3-monthly until the start of radiation therapy. The baseline median volume was 82 cc, with a median reduction of 31% after 3 months of ADT. Between 3 and 6 months, an additional median volume reduction of 9% was observed. The effect was more pronounced in large prostates (> 60 cc). After 6 months no significant reduction of volume was seen. From this study we have concluded that the most significant volume reduction is achieved after 3 months of ADT, and the maximum reduction after 6 months. Therefore, the optimal duration of neoadjuvant ADT for prostate volume reduction seems 6 months. In **chapter 8** the predictive value of PSA for progression, and the role of testosterone for QOL in patients on continuous or intermittent ADT for metastatic prostate cancer are described. As expected, patients with high baseline PSA, pain, and high PSA nadir appear to have a poor prognosis with ADT. Furthermore, even patients with a low PSA nadir, after a 6-month induction course of maximal androgen blockade, did significantly worse on intermittent therapy than on continuous ADT. Also, testosterone level remains low for long periods of time after withdrawal of hormones. The incomplete testosterone recovery, after a 6-month induction course, may explain why quality of life (QOL) was not improving in the off-treatment phase. Although more side effects were seen in the continuous treatment group no QOL differences were found between groups. Therefore, intermittent hormonal therapy seems a suboptimal treatment option for many metastatic prostate cancer patients.

Hoofdstuk 9 Samenvatting

In Nederland wordt jaarlijks bij meer dan 9.000 mannen prostaatkanker geconstateerd. Er is een trend waarneembaar naar het diagnostiseren op jongere leeftijd en vaker worden de tumoren in een vroeg stadium behandeld. Uiteindelijk zal dit mogelijk de kankerspecifieke overleving verbeteren, maar momenteel is dat nog onvoldoende duidelijk. De keerzijde van agressief behandelen is dat er bijwerkingen te verwachten zijn voor de patiënt die altijd meegewogen moeten worden tijdens de bespreking van het behandelvoorstel. Het doel van dit proefschrift is een evaluatie te verrichten van de ontwikkelingen in prostaatkankerbehandeling die zich richten op de vermindering van complicaties met behoud van de oncologische resultaten.

In **hoofdstuk 2** wordt de ontwikkeling van 'high-precision' radiotherapie met behulp van goudmarkers beschreven. Uit klinische studies is een dosis-respons relatie gebleken voor radiotherapie van prostaatcarcinoom. Dosis-escalatie kan mogelijk echter door de blootstelling aan hoge doses de toxiciteit van de omliggende weefsels, zoals de blaas, het rectum en anale kanaal verhogen. Bovendien is de prostaat een bewegend orgaan dat dagelijks een paar millimeter verplaatst. Samen met de variaties in positionering van de patiënt vergt dit bepaalde behandelmarges rond de prostaat voor een adequate dekking van het doelorgaan. Goudmarkers in de prostaat zijn uitstekend zichtbaar op de dagelijkse elektronische 'portal images' tijdens de bestraling. Hierdoor zijn een exacte verificatie en correctie van de prostaatpositie en daardoor kleinere marges mogelijk. De invloed van goudmarkers op het behandelvolume en op de bestralingsdosis van de omliggende weefsels werd in deze studie onderzocht. Om de afname van het planning doelvolume (PTV) te tonen werden drie in de historie gebruikte behandelingsmarges gereconstrueerd: PTV 10 mm (zonder goudmarkers), PTV 7 mm (met markers) en PTV 7/5 mm (met markers en online correctie). Het behandelingsvolume en de bestralingsdoses werden met het computertomografie (CT) scanningsysteem berekend. Door het gebruik van goudmarkers werd een significante afname van PTV van 27% bereikt. Dientengevolge werd ook een afname gezien in de gemiddelde bestralingdosis van 17% (±4.5%) van de blaas, 19% (±4.7%) van het anale kanaal en 12% (±3%) van het rectum. Hoewel het zeer aannemelijk is te veronderstellen dat goudmarkers een positief effect hebben op de late toxiciteit van bestraling dient dit verder onderzocht te worden in klinische trials.

Aangezien de goudmarkerimplantatieprocedure invasief is, is deze alleen te rechtvaardigen als de complicaties hiervan gering zijn. In **hoofdstuk 3** worden daarom de complicaties en de risicofactoren voor complicaties van transrectaal geïmplanteerde goudmarkers geanalyseerd. Bij 209 opeenvolgende mannen met gelokaliseerd prostaatcarcinoom werden onder echogeleide vier kleine goudmarkers geplaatst en de complicaties hiervan werden geanalyseerd met vragenlijsten. Bij 13 mannen (6.2%) kwam een matig ernstige complicatie voor die bestond uit pijn of koorts die kon worden behandeld met orale medicatie. Bij 1.9% van de mannen werd een geringe mictieklacht gezien. Andere geringe voorbijgaande complicaties zoals hematurie meer dan 3 dagen, hematospermie en rectaal bloedverlies kwamen voor bij respectievelijk 3.8%, 18.5% en 9.1% van de mannen. Bij patiënten met een uitgebreid tumorstadium, jonge leeftijd en korte duur van de hormonale behandeling werden vaker complicaties gezien. De conclusie is dat de transrectale implantatie van goudmarkers veilig is en goed wordt verdragen door de patiënt.

Een potentiële curatieve behandelmogelijkheid van een biochemisch lokaal recidief na radicale prostatectomie is 'salvage' radiotherapie van de prostaatloge. Patiënten met positieve snijvlakken en een hoogrisico prostaatcarcinoom hebben voordeel van adjuvante radiotherapie. Voor deze specifieke patiënten is recent de beeldgeleide radiotherapie geïntroduceerd met goudmarkerimplantatie in de prostaatloge en elektronische 'portal imaging'. De ervaring met deze implantatietechniek is beperkt en er zijn vooralsnog geen grote series beschreven. In **hoofdstuk 4** worden de techniek en het aantal complicaties van echogeleide transrectale implantatie van goudmarkers na radicale prostatectomie beschreven. Bij 77 opeenvolgende mannen met een biochemisch recidief of positieve chirurgische snijvlakken na een radicale prostatectomie en hoogrisico prostaatkanker werden 3 kleine goudmarkers geïmplanteerd in de prostaatloge. De haalbaarheid van markerplaatsing werd geanalyseerd en de markermigratie werd gescoord met behulp van beeldvormende technieken. De patiënten vulden

vragenlijsten in voor de registratie van het aantal complicaties. Weinig ernstige complicaties waren onder meer rectaal bloedverlies gedurende een dag bij 10 patiënten (13%) en mictieklachten bij een patiënt. Weinig ernstige complicaties zoals een ongemakkelijk gevoel rectaal met spontaan herstel binnen 7 dagen (n=2), misselijkheid gedurende twee dagen (n=1), een ongemakkelijk gevoel in de buik (n=1) en pijn waarvoor pijnstillers noodzakelijk waren (n=4) werden bij 8 patiënten gezien (10%). De gemiddelde VAS score bij implantatie, op een schaal van 1 tot 10, was 3.7. Postoperatieve stricturen, die als maat voor fibrose van het operatiegebied werden beschouwd, leidden niet tot significant meer pijn tijdens de implantatie. Transrectale goudmarkerimplantatie in de prostaatloge, als onderdeel van de bestraling na radicale prostatectomie, is daarom haalbaar en veilig. Vooral bij jonge patiënten staat de pijn iets meer op de voorgrond dan tijdens de goudmarkerplaatsing in de prostaat zelf en daarom is het te adviseren om vooraf pijnstillers te geven. Er werden overigens geen risicofactoren voor bloedingen en pijn gevonden.

In **hoofdstuk 5** wordt een literatuuroverzicht gegeven, na screening van Pub med, van primaire en 'salvage' cryochirurgie van de prostaat. Hieruit blijkt dat met de introductie van gasgebaseerde derde-generatie cryotechnologie het aantal bijwerkingen significant is afgenomen vergeleken met oudere cryochirurgie technieken met behoud van oncologische resultaten. Het optreden van ernstige complicaties zoals rectourethrale fistels (< 1%) is bijna verdwenen, maar het aantal patiënten met erectiele disfunctie blijft hoog (90%). Bij 'salvage' cryochirurgie zijn meer bijwerkingen te verwachten zoals een gemiddeld incontinentie percentage van 8% en fistels tot 3.4%. Desondanks blijft deze minimaal invasieve behandeling een optie voor recidief prostaatcarcinoom na radiotherapie aangezien de 'salvage' radicale prostatectomie een hoog complicatiegetal kent. De huidige data in de literatuur over cryochirurgie zijn echter van 'low-level evidence', wat bij consultatie van de patiënt verteld moet worden. Focale cryochirurgie wordt als experimenteel beschouwd maar het is een interessante nieuwe ontwikkeling in de cryochirurgie met als oogmerk vermindering van complicaties. Het verrichten van gerandomiseerde studies met langetermijn follow-up moet worden gestimuleerd om uiteindelijk de rol van cryochirurgie voor de behandeling van gelokaliseerde prostaatkanker duidelijk te maken.

Hoofdstuk 6 biedt een literatuuroverzicht van de rol van androgene deprivatietherapie (ADT) in de neoadjuvante en intermitterende setting. Dit hoofdstuk is een introductie voor de klinische studies die in hoofdstuk 7 en 8 worden besproken. Neoadjuvante hormonale therapie geeft bij lokaal uitgebreide prostaatkanker en hoogrisico patiënten een betere lokale tumorcontrole en ziektespecifieke overleving als het gecombineerd wordt met radiotherapie vergeleken met alleen radiotherapie. Het moet daarom als standaardtherapie worden beschouwd bij deze patiëntengroepen. De noodzakelijke duur van de voorbehandeling is echter een punt van discussie en ligt ergens tussen de 3–6 maanden. De rol van neoadjuvante ADT voor chirurgie is beperkt. Bij patiënten met uitgebreide of gemetastaseerde prostaatkanker is hormonale therapie in een intermitterend schema haalbaar gebleken. De progressievrije overleving lijkt vergelijkbaar met die van patiënten die continue ADT krijgen. Door de intervallen waarin geen therapie wordt gegeven is er een reductie van kosten mogelijk. Er is een verbetering van seksuele functie en wellicht kwaliteit van leven haalbaar. Het effect van intermitterende behandeling op de complicaties van hormonale therapie op lange termijn, zoals osteoporose en metaboolsyndroom, is onbekend. **Hoofdstuk 7** gaat over de optimale duur van neoadjuvante ADT voor de reductie van prostaatvolume voorafgaand aan radiotherapie. Bij een zeer groot prostaatvolume kan ADT voor radiotherapie een 'downsizing' effect van de prostaat geven ter verbetering van de dosimetrische parameters en een vermindering van bestralingsdosis op de omliggende weefsels. Bij 20 opeenvolgende patiënten met een cT2–3No/xMo prostaatcarcinoom, die radiotherapie gingen krijgen, werd gedurende 9 maanden neoadjuvante ADT gegeven. Elke 3 maanden werd een CT scan onderzoek verricht voor de bepaling van het prostaatvolume tot aan de start van de radiotherapie. Het uitgangsvolume was mediaan 82 cc met een mediane reductie van 31% na 3 maanden ADT. Tussen 3 en 6 maanden werd een additionele mediane volumereductie van 9% gezien. Bij grote prostaten (> 60 cc) was het effect duidelijker. Na 6 maanden werd geen significante afname van volume gezien. De conclusie van deze studie was dan ook dat de meest significante volumereductie na 3 maanden ADT optreedt en de maximale reductie na 6 maanden. De optimale duur van neoadjuvante ADT voor de reductie van het prostaatvolume lijkt dan ook 6 maanden te zijn. In **hoofdstuk 8** worden de predictieve waarde voor progressie van PSA en de

rol van testosteron voor de kwaliteit van leven van patiënten beschreven tijdens continue of intermitterende ADT voor gemetastaseerd prostaatcarcinoom. Volgens verwachting bleken patiënten met een hoog uitgangs-PSA, pijn en een hoge PSA nadir een slechte prognose te hebben met ADT. Zelfs patiënten met een lage PSA nadir, na 6 maanden inductietherapie met maximale androgene blokkade, deden het significant slechter op intermitterende therapie dan op continue ADT. Verder bleef testosteron laag gedurende lange periodes na het onttrekken van de hormonen. Het incomplete herstel van testosteron na de 6 maanden inductieperiode, verklaart misschien waarom de kwaliteit van leven niet verbeterde in de periode waarin geen hormonen werden gegeven. Er werden geen verschillen in kwaliteit van leven tussen de groepen gevonden, ondanks het feit dat meer bijwerkingen optraden in de continue behandelgroep. Intermitterende hormonale therapie lijkt daarom een suboptimale behandeling voor veel patiënten met gemetastaseerde prostaatkanker.

Chapter

10

Future perspectives
Toekomstverwachtingen

Chapter 10 Future perspectives

Image-guided radiotherapy

Oncological aspects & toxicity

For better oncological outcome after prostate radiotherapy dose escalation has been introduced. In several randomized trials, an increased radiation dose led to significantly improved biochemical progression-free survival, but also to more gastro-intestinal toxicity [1-3]. The aim of new radiation techniques for prostate cancer is an improved tumor control with low complication rates. One of these new techniques is intensity-modulated radiation therapy (IMRT), which may reduce acute and late toxicity by precisely focusing the high-dose to the prostate with subsequently decreased doses to surrounding tissues [4]. For this highly conformal radiation therapy, the daily target localization procedure is the cornerstone of the approach. A small shift in prostate position can lead to significant under dosage of the target volume. In recent years, fiducial gold marker implantation has become a standard of care for daily target position verification and correction. In this thesis, the reduction of target volume due to gold markers and the subsequent beneficial effect on radiation doses to surrounding healthy tissues are described, suggesting that marker application might reduce toxicity rates. However, although the advantages of gold marker-based position verification and correction of the prostate for high-precision radiotherapy are evident, no randomized studies have been performed to confirm this. These studies will probably never be performed, and therefore future research should focus on the long-term clinical outcome, i.e., tumor control rate and normal tissue toxicity, in patients receiving both primary radiotherapy and radiotherapy in the adjuvant post prostatectomy setting, with daily gold marker-based correction procedures.

Gold markers may also have a future role in focal prostate radiotherapy, for example magnetic resonance spectroscopy (MRS)-guided brachytherapy with a boost to a dominant intraprostatic lesion (DIL). The tumor control probability is shown to be high, with the potential to spare normal tissues, especially the urethra [5]. Implanting a gold marker MRI-guided inside the DIL could help for daily position verification during the procedure without the need of daily magnetic resonance imaging.

Complications

Complication rates of gold marker implantation should be low for high acceptance of the patients and to prevent deterioration of quality of life. In this thesis, we have shown that the complication rates are indeed low, and they seem to be acceptable for their purpose. Potential serious complications, like urosepsis, are effectively prevented by antibiotic prophylaxis [6]. Increasing antibiotic-resistant Escherichia coli bacteria have been observed worldwide [7], and growing concern exists about the number of septic complications after prostate biopsies. Therefore, alternative prophylactic antibiotics for gold marker implantation should be investigated. The pain experienced during marker implantation is high in only a small percentage of patients. From prostate biopsy studies it is known that young patients have more pain during the procedure than older ones [8,9]. In our study on post prostatectomy gold marker implantation a similar trend was observed. It would be of interest to investigate further if an age cut-off can be defined for prophylactic analgesics. With the implantation of intraprostatic gold markers this trend was not found. The minimal invasive aspect of gold marker implantation makes it highly acceptable to patients, but when serious complications are increasing this may change.

New markers

Refinements of radiation technique have been introduced and other means of image-guided radiotherapy were developed. For instance, the Calypso 4D localization system, consisting of an electronic array which is placed above the patient, localizes and tracks electromagnetic transponders, implanted in the prostate, that respond to electromagnetic signals. This results in continuous information about the transponders' position in three dimensions, thereby representing the intrafraction prostate motion. These transponders have the same long-term stability as gold markers [10]. In fact, treatment with electromagnetic prostate positioning and monitoring is a continuous, real-time adaptive way of radiotherapy [11]. This may allow for even smaller treatment margins than with gold markers. Clinical studies have shown that transponders are implanted using the same procedure as for gold markers, with similar and acceptable complication

rates [12,13]. The transponders are inserted with a 14-gauge needle, which could result in more pain during implantation because of the larger diameter of the needle, but the data are hard to compare with our results because the literature does not provide information about VAS scores or the need for analgesics [11]. Furthermore, the implantation of electromagnetic transponders following radical prostatectomy has been reported very recently [14]. Complications after the implantation procedure seem minor but more data on this subject are expected in the nearest future.

Cryosurgery

Curative prostate cancer treatment leads to a substantial number of complications, like incontinence and erectile dysfunction. Therefore, new minimal invasive treatment modalities, i.e., cryosurgery and high-intensity focused ultrasound (HIFU) have been developed as an alternative for radical prostatectomy and radiotherapy. Complication rates of salvage radical prostatectomy, after local radiotherapy recurrent disease, are even higher than in primary surgery. Especially incontinence rates are significant and up to 45% of patients [15]. When developing alternative treatment options, oncological results should not be compromised, and complications should be less. Indeed, with the latest third-generation cryosurgery machines, the results are comparable to previous techniques, and complication rates have improved. In large patient series treated with cryosurgery the complication rates were low. However, one should realize that these reports are biased because they come from highly experienced centers. The introduction of this treatment should be done with the utmost care not to harm the patient. Cryosurgery is a technically demanding procedure and has a long learning curve [16]. It should be advocated to treat patients in clinical trials, and initial procedures must be performed after adequate training and preferably be accompanied by an expert in the field.

There is a growing interest in focal therapy of prostate cancer, especially in the light of stage shift and younger age of the patients. From autopsy studies it is known that up to 20%–30% of prostate cancers are solitary tumors [17]. These

patients could benefit from focal cryosurgery targeting one lobe only. Also, the feasibility of nerve-sparing cryosurgery by active warming of the neurovascular bundle has been evaluated in an experimental animal setting [18]. Few patients so far have been actually treated with focal cryosurgery, and this treatment should therefore be regarded as experimental. Further, modern imaging techniques, like dynamic contrast enhanced MRI and MRS with image-guided biopsies will play an important role in diagnosing the disease, in prostate tumor delineation during treatment and in follow-up. To get a clear inside in the oncological results of cryosurgery, treatment should be monitored by histological examination, because PSA and imaging alone seem to be insufficient. For now, cryosurgery appears to be a good alternative option for salvage procedures. We need long-term follow-up of oncological outcome in multicenter studies to evaluate the performance of primary and focal cryosurgery.

Hormonal therapy

Neoadjuvant androgen deprivation therapy

In prostate cancer, androgen deprivation therapy (ADT) can be administered combined with radiotherapy to improve oncological control and for downsizing reasons. In our series, the optimal duration of neoadjuvant ADT from a downsizing point of view was 6 months. There is, however, conflicting evidence for overestimation of prostate volume measurement by computed tomography (CT), compared to ultrasound and MRI, which could lead to longer continuation of ADT than necessary. This can be corrected for with CT-MRI matching, but this modality is not routinely available in most institutions. The clinical implications of overestimation of prostate volume need further research, and consideration of costs for extra imaging procedures should be included.

From an oncological point of view, in several randomized trials for locally advanced and high-grade localized disease an improved local tumor control rate, disease-free survival, distant metastases-free rate [19,20], and even overall survival [21-24] were shown with ADT combined with radiotherapy. Bolla et al. [21] showed that long-term treatment for high-risk disease (d'Amico classification) should consist

of 3 years of adjuvant ADT. The advantages of ADT in low and intermediate risk disease have been questioned. New randomized trials on the optimal duration of neoadjuvant ADT showed that patients with high-risk disease benefit from longer neoadjuvant ADT, but in low-, and intermediate risk patients 3-months [19,25] or 4-months [26] of neoadjuvant ADT seemed enough to improve overall survival. Whether long-term adjuvant ADT compared to short-term neoadjuvant ADT can provide an additional survival benefit for patients with high-risk prostate cancer requires further study. Reports about the increased risk of diabetes, cardiovascular disease, and accelerated time to cardiac death in men exposed to even a short course of ADT [27,28] have provoked additional discussion of the true benefit of this treatment regimen. Some have shown that treatment-related morbidity was not increased, 5 years after randomization, for patients on 3, and 6 months of ADT compared with patients without neoadjuvant ADT [19]. Therefore, 6 months of neoadjuvant ADT combined with radiotherapy seems adequate for men who are at risk for micrometastatic disease and with pre-existing metabolic comorbidities that could be exacerbated by prolonged ADT.

A multicenter randomized study initiated by the Canadian Urologic Oncology Group, comparing ADT with or without radiotherapy, for patients with locally advanced prostate cancer, addressed whether radiotherapy adds to overall survival [29]. Formal publication is awaited, but preliminary reports have shown a substantial benefit in overall and disease specific survival for the combined treatment modality. The value of neoadjuvant treatment in the context of high-radiation doses remains unproven and needs further study. The discussion is ongoing whether dose-escalated radiotherapy techniques can improve survival and if long-term adjuvant ADT is still necessary with higher radiation doses. So far, several phase III trials have demonstrated that higher radiation doses reduce the risk of biochemical failure [30,31], but none have demonstrated differences as significant as those shown in, for instance, the RTOG 8610 trial [32]. Dose-escalation harbors the risk of increased toxicity to surrounding organs and downsizing of the prostate by ADT may be of paramount significance, but this needs reconfirmation. Therefore, more research is needed to show the exact impact of prostate volume reduction on rectal volumes receiving high-dose radiation. Furthermore, the question whether the use of neoadjuvant luteinizing-hormone releasing hormone (LHRH) agonist alone instead of the combination with antiandrogens may be enough for a survival benefit is unanswered.

In conclusion, administering 6 months of neoadjuvant ADT combined with radiotherapy for locally advanced or high-risk prostate cancer, without nodal metastasis, seems advisable to improve oncological outcome, and to reduce volume in large prostates. This may enable sparing of surrounding healthy tissues. Side effects may be significant even in the setting of short neoadjuvant treatment and therefore low- and intermediate risk patients should not routinely receive neoadjuvant ADT, or for a period of only 3 months, except in very large prostates for improved dosimetric parameters. These patients may benefit more from high-dose radiation and future research will hopefully reveal if combined ADT is still necessary.

Intermittent androgen deprivation therapy

In metastatic prostate cancer patients, ADT is often administered for long periods of time. The side effects of hormonal therapy are considerable, which resulted in the development of intermittent androgen deprivation therapy (IAD). In our study, we have identified patient groups that are not suitable for intermittent therapy, based on certain predictive variables for progression. Others have found similar findings and therefore it seems advisable to reserve intermittent hormonal therapy for patients with moderately elevated PSA and a relatively low burden of disease, preferably non-metastatic. Patients with local recurrent disease or those who are unfit for curative treatment could benefit from IAD, although these patients might not need hormone therapy for several years without affecting survival. Indeed, one study has shown no difference in prostate cancer specific survival in patients, who were unfit for radical therapy, and were randomized for immediate or deferred ADT when progression occurred [33]. In that study, 26% of patients in the delayed arm died without ever needing treatment. This suggests that active surveillance may actually be a good alternative treatment for ADT, or even for IAD in patients with low burden disease. In this setting we need further evidence that intermittent hormonal therapy is needed for better survival, as it actually might harm the patient because of side effects. An alternative option could be to administer antiandrogens alone to avoid side effects of chemical castration.

In general, patients needing hormonal treatment who have bad predictive factors might benefit more of an early switch to alternative treatments and future research should focus on currently available new medications for this patient group. Of course, survival is the only important endpoint in prostate cancer therapy with all others being surrogate endpoints. Our study was underpowered and follow-up was too short to show a survival difference, and we used clinical progression as a surrogate endpoint. Future research and ongoing trials on intermittent therapy might provide us with more information on survival differences. In fact, new phase III trials seem necessary to confirm that IAD does not jeopardize prostate cancer specific survival. We found that patients with low PSA nadir had a significantly higher risk of progression with IAD than with continuous ADT. So, withholding ADT seems to actually harm these patients. This is a remarkable outcome and is contradictory to the finding that PSA nadir is a strong predictor of survival [34]. To our knowledge this has not been reported before and needs validation in other clinical trials.

Apparently, in our study IAD had no QOL benefit probably because of incomplete testosterone recovery in the off-treatment phase, although side effects were less. This is hard to explain and needs further research. We should realize that study outcomes of QOL and side effects measurement are biased because double blind placebo-controlled studies have never been performed. The knowledge of being in the intermittent arm can influence the side effect profile. The long castrate level, after LHRH agonists induction course, is another factor influencing QOL measurements. Future research may therefore focus on intermittent therapy with antiandrogens only. Data on the long-term consequences for side effects of IAD are unavailable, but are expected in the near future when ongoing trials have reached maturity.

Hoofdstuk 10 Toekomstverwachtingen

Beeldgeleide radiotherapie

Oncologische aspecten & toxiciteit

Dosis-escalatie is geïntroduceerd om de oncologische resultaten van radiotherapie van de prostaat te verbeteren. In verschillende gerandomiseerde studies leidde een hogere bestralingsdosis tot een significant betere biochemische progressievrije overleving, maar ook tot meer gastro-intestinale bijwerkingen [1-3]. Het doel van nieuwe bestralingstechnieken voor prostaatkanker is de verbetering van de lokale tumorcontrole en vermindering van complicaties. Een van deze nieuwe technieken is intensiteit-gemoduleerde radiotherapie (IMRT), waarbij de acute en late toxiciteit verminderd kunnen worden door de precieze instelling van de hoge dosis op de prostaat en dientengevolge een vermindering van de hoge dosis op de omliggende weefsels [4]. De dagelijkse lokalisatieprocedure van het bestralingsdoel is bij deze conformele bestralingstherapie een essentieel onderdeel van de benadering. Een kleine verplaatsing in de positie van de prostaat kan leiden tot een significante onderdosering van het doelvolume. In de laatste jaren is de implantatie van goudmarkers een standaard manier geworden voor het dagelijks verifiëren en corrigeren van de positie van het bestralingsdoel. In dit proefschrift worden de afname van het doelvolume door het gebruik van goudmarkers en het positieve effect op de bestralingsdosis van de omgevende gezonde weefsels beschreven. Dit suggereert ook dat goudmarkergebruik de toxiciteit vermindert. Hoewel de voordelen van positieverificatie en correctie van de prostaat met behulp van goudmarkers voor precisie-radiotherapie evident zijn, zijn tot nog toe geen gerandomiseerde studies verricht die de afname van toxiciteit bevestigen. Omdat dit soort studies waarschijnlijk nooit zal worden verricht moet toekomstig onderzoek, bij patiënten die zowel primaire radiotherapie als radiotherapie in de adjuvante setting na een radicale prostatectomie krijgen met de dagelijkse op goudmarker gebaseerde correctieprocedure, zich richten op de klinische uitkomsten op lange termijn zoals de lokale tumorcontrole en de toxiciteit op normale weefsels.

Goudmarkers zullen mogelijk in de toekomst ook een rol krijgen bij focale radiotherapie van de prostaat zoals bij magnetische resonantiespectroscopie (MRS)-geleide brachytherapie met een 'boost' op een dominante intraprostatische laesie (DIL). Er werd al aangetoond dat de mogelijkheden van lokale tumorcontrole groot zijn met potentiële bescherming van de normale weefsels zoals de urethra [5]. Het MRI-geleid implanteren van een goudmarker in de DIL zou kunnen helpen bij het dagelijks verifiëren van de tumorpositie tijdens de procedure zonder de noodzaak om ook dagelijks MRI te hoeven inzetten.

Complicaties

Het aantal complicaties van goudmarkerimplantatie moet laag zijn voor een hoge acceptatiegraad van de patiënten en om een aantasting van de kwaliteit van leven te voorkomen. In dit proefschrift wordt getoond dat het aantal complicaties inderdaad laag is en ook acceptabel lijkt met het oog op het doel van de plaatsing. Potentiële ernstige complicaties zoals urosepsis worden effectief voorkomen door middel van antibioticumprofylaxe [6]. Er wordt wereldwijd echter een toenemende antibioticaresistentie van Escherichia coli bacteriën gezien [7] en daardoor nemen de zorgen over het aantal septische complicaties na bijvoorbeeld prostaatbiopten toe. Alternatieve antibioticumprofylaxe voor goudmarkerimplantatie moet daarom worden onderzocht. Ernstige pijn tijdens markerplaatsing is slechts in een klein percentage patiënten aantoonbaar. Uit prostaatbiopsiestudies is bekend dat jonge patiënten meer pijn hebben tijdens de procedure dan ouderen [8,9]. Een soortgelijke trend werd gezien in onze studie naar goudmarkerimplantatie in de prostaatloge. Het zou interessant zijn om verder onderzoek te verrichten naar een afkapwaarde van de leeftijd voor preventieve pijnstilling. Bij de implantatie van goudmarkers in de prostaat werd deze trend overigens niet gezien. Het minimaal invasieve karakter van goudmarkerimplantatie maakt het een zeer acceptabele procedure voor patiënten, maar als het aantal ernstige bijwerkingen toeneemt, zou dit weleens kunnen veranderen.

Nieuwe markers

De bestralingstechnieken zijn verder verfijnd en andere vormen van beeldgeleide radiotherapie werden ontwikkeld. Een voorbeeld is het Calypso 4D lokalisatiesysteem dat bestaat uit een elektronische opstelling die boven de

patiënt wordt gepositioneerd en waarmee elektromagnetische bakens in the prostaat, die op elektromagnetische signalen reageren, worden gelokaliseerd. Hierdoor is er continu informatie beschikbaar over de 3D positie van de bakens en daardoor is de beweging van de prostaat tijdens iedere bestralingsfractie bekend. Deze bakens hebben dezelfde stabiliteit op lange termijn als goudmarkers [10]. De behandeling met elektromagnetische positionering en het monitoren van de prostaat is feitelijk zelfs een continue, 'real-time' en adaptieve manier van radiotherapie [11]. Hierdoor zijn waarschijnlijk nog kleinere behandelingsmarges mogelijk dan met goudmarkers. Uit klinische studies is gebleken dat de bakens volgens dezelfde methode worden geïmplanteerd als goudmarkers, met vergelijkbare en acceptabele complicatiegetallen [12,13]. De bakens worden geplaatst met een 14-gauge naald, die door de grotere diameter mogelijk meer pijn geeft tijdens implantatie, maar de beschikbare data hierover zijn moeilijk vergelijkbaar met onze resultaten omdat in de literatuur geen informatie beschikbaar is over VAS scores of de behoefte aan pijnstilling naderhand [11]. Verder is zeer recent de implantatie van elektromagnetische bakens na radicale prostatectomie beschreven [14]. De complicaties na deze implantatieprocedure lijken minimaal, maar in de nabije toekomst worden meer gegevens over dit onderwerp verwacht.

Cryochirurgie

Curatieve behandeling van prostaatkanker leidt in een aanzienlijk aantal gevallen tot complicaties, zoals incontinentie en erectiele disfunctie. Om die reden zijn nieuwe minimaal invasieve behandelingen, zoals cryochirurgie en hoge-intensiteit gefocusseerde echografie (HIFU) ontwikkeld, als alternatief voor de radicale prostatectomie en radiotherapie. De aantallen complicaties na 'salvage' radicale prostatectomie, voor een lokaal recidief na radiotherapie, zijn veel hoger dan na primaire chirurgie. Vooral het percentage incontinentie is significant en loopt op tot 45% van de patiënten [15]. Bij de ontwikkeling van alternatieve behandelingen moet het aantal complicaties juist lager liggen, met behoud van oncologische resultaten. Met de laatste derde-generatie cryochirurgie-apparatuur zijn de resultaten vergelijkbaar met eerdere technieken en de complicatiegetallen zijn verbeterd. Bij grote patiëntenseries zijn de complicaties na cryochirurgie laag

gebleken. Men moet zich echter realiseren dat deze resultaten een bias vertonen omdat zij zijn verkregen uit centra met uitgebreide cryochirurgie ervaring. De introductie van deze therapie moet met grote voorzichtigheid worden omkleed om de patiënt niet te schaden. Cryochirurgie is een technisch veeleisende procedure en het heeft een lange leercurve [16]. Het zal verder bevorderd moeten worden om patiënten in klinische trials te behandelen en het wordt geadviseerd om de procedure in het begin bij voorkeur in het bijzijn van een erkende expert op dit gebied en slechts na adequate training uit te voeren.

De interesse voor focale therapie van prostaatkanker groeit, zeker in het licht van de verschuiving van stadium en leeftijd van de patiënt bij diagnosestelling. Uit obductiestudies is gebleken dat het bij 20%–30% van alle prostaatkankerpatiënten solitaire tumoren betreft [17]. Deze patiënten kunnen voordeel hebben van focale cryochirurgie gericht op één prostaatkwab. Verder is de haalbaarheid van zenuwsparende cryochirurgie door middel van actieve verwarming van de neurovasculaire bundel geëvalueerd in een dierexperimenteel model [18]. Tot nu toe zijn slechts enkele patiënten daadwerkelijk behandeld met focale cryochirurgie en daarom moet deze therapie als experimenteel worden beschouwd. Moderne beeldvormende technieken zoals dynamische contrast versterkte MRI en MRS, met beeldgeleide biopsie, zullen een belangrijke rol spelen bij het diagnostiseren van de ziekte, bij de afbeelding van de prostaattumor tijdens de behandeling en tijdens de follow-up. Voor een goed inzicht in de oncologische resultaten van cryochirurgie moet de behandeling worden geëvalueerd door middel van histologie, omdat PSA en beeldvorming alleen nog onvoldoende zekerheid geven. Cryochirurgie lijkt op dit moment een goede alternatieve behandeloptie voor 'salvage' procedures. Langetermijn follow-up van oncologische resultaten in multicentrische studies is echter onontbeerlijk ter evaluatie van het succes van primaire en focale cryochirurgie.

Hormonale therapie

Neoadjuvante androgene deprivatietherapie

Androgene deprivatietherapie (ADT) kan bij prostaatkanker worden toegepast

in combinatie met radiotherapie ter verbetering van de oncologische controle en om de prostaat te verkleinen. Vanuit het oogpunt van prostaatverkleining is de optimale duur van neoadjuvante ADT in onze serie 6 maanden. Er zijn echter tegenstrijdige berichten in de literatuur over overschatting van prostaatvolume meting door middel van CT in vergelijking met echografie en MRI, die zou kunnen leiden tot het langer continueren van ADT dan nodig is. Dit is te corrigeren met de combinatie CT-MRI, maar deze is niet routinematig beschikbaar in de meeste klinieken. Voor de implicaties van overschatting van het prostaatvolume in de kliniek is verder onderzoek noodzakelijk en hierbij dient ook het kostenaspect van extra beeldvormende procedures te worden meegenomen.

Vanuit een oncologisch standpunt is er in verschillende gerandomiseerde trials voor lokaal uitgebreid en hooggradig gelokaliseerd prostaatcarcinoom een verbeterde lokale controle, ziektevrije overleving, metastasevrije overleving [19,20] en ook totale overleving [21-24] aangetoond door gebruik van ADT in combinatie met radiotherapie. Bolla en anderen [21] toonden aan dat langdurige hormonale behandeling voor hoogrisico ziekte (d'Amico classificatie) uit 3 jaar adjuvante ADT moet bestaan. De voordelen van ADT voor laag- en intermediair-risico ziekte zijn meer een punt van discussie. Nieuwe gerandomiseerde studies naar de optimale duur van neoadjuvante ADT hebben aangetoond dat patiënten met hoogrisico prostaatkanker voordeel hebben van langere neoadjuvante ADT, maar in laag- en intermediair-risico is 3 [19,25] of 4 maanden [26] neoadjuvante ADT waarschijnlijk genoeg voor een verbetering van de totale overleving. Er is verder onderzoek nodig om te verduidelijken of langdurige adjuvante ADT vergeleken met kortdurende neoadjuvante ADT een extra overlevingsvoordeel oplevert bij patiënten met hoogrisico prostaatkanker. De berichtgeving over het verhoogde risico op diabetes, cardiovasculaire ziekten en een verkorting van de tijd tot overlijden door cardiaal falen bij mannen die slechts kort worden blootgesteld aan ADT [27,28] heeft meer discussie los gemaakt over het werkelijke voordeel van deze behandelingsstrategie. Er is echter door enkele onderzoekers aangetoond dat 5 jaar na randomisatie de behandelingsgerelateerde morbiditeit niet was toegenomen bij patiënten met 3 en 6 maanden ADT in vergelijking met patiënten zonder neoadjuvante ADT [19]. Daarom lijkt 6 maanden neoadjuvante ADT in combinatie met radiotherapie zinvol en verantwoord bij mannen die een hoog

risico hebben op micrometastasen en met pre-existente metabole comorbiditeit die verergerd kan worden door langdurige ADT behandeling.

Er werd een multicentrische gerandomiseerde studie verricht op initiatief van de Canadian Urologic Oncology Group ter vergelijking van ADT met radiotherapie en alleen ADT bij patiënten met lokaal uitgebreid prostaatcarcinoom met als primair eindpunt de bijdrage van radiotherapie aan de totale overleving [29]. De formele publicatie is nog niet beschikbaar, maar uit de voorlopige resultaten komt een aanzienlijk voordeel in totale en ziektespecifieke overleving voor de combinatietherapie. De waarde van neoadjuvante behandeling bij hogedosis radiotherapie is nog onduidelijk en hiervoor is meer onderzoek vereist. De discussie is gaande of radiotherapietechnieken met dosis-escalatie de overleving kunnen verbeteren en of langetermijn adjuvante ADT nog wel noodzakelijk is bij deze hogere bestralingsdoses. Tot nu toe hebben verschillende fase III trials bewezen dat hogere doses van bestraling het risico op biochemisch recidief reduceren [30, 31], maar een verschil zo groot als bijvoorbeeld in de RTOG 8610 studie, is nooit aangetoond [32]. Het risico van dosis-escalatie is een toename van de toxiciteit op de omliggende weefsels en daarom is verkleining van het prostaatvolume door middel van ADT wellicht van doorslaggevend belang, hoewel dit nog in verder onderzoek bevestigd moet worden. Aanvullend onderzoek is dan ook vereist om de precieze invloed van prostaatvolume reductie op het rectumvolume, dat een hogedosis bestraling krijgt, aan te tonen. Ook de vraag of het gebruik van alleen een neoadjuvante LHRH agonist in plaats van de combinatie met een antiandrogeen voldoende is voor een overlevingswinst is nog onbeantwoord.

Concluderend is het te adviseren om voor lokaal uitgebreide en hoogrisico prostaatkanker, zonder lymfekliermetastasen, 6 maanden neoadjuvante ADT in combinatie met radiotherapie te geven ter verbetering van de oncologische resultaten en ter verkleining van het volume van de prostaat. Hierdoor wordt wellicht het omliggende gezonde weefsel gespaard van hogedosis bestraling. Zelfs bij kortdurende neoadjuvante behandeling kunnen de bijwerkingen aanzienlijk zijn en daarom wordt dit niet routinematig of voor slechts een periode van 3 maanden geadviseerd bij laag- en intermediair-risico patiënten, tenzij het prostaatvolume erg groot is en een verbetering van de dosimetrische parameters

wordt nagestreefd. Deze patiënten hebben waarschijnlijk meer voordeel van hogedosis bestraling en hopelijk komt uit toekomstig onderzoek naar voren of een combinatie met ADT nog noodzakelijk is.

Intermitterende androgene deprivatietherapie

Bij patiënten met gemetastaseerd prostaatcarcinoom wordt vaak langdurige ADT gegeven. De bijwerkingen van hormonale therapie zijn aanzienlijk en dit heeft geleid tot de ontwikkeling van intermitterende androgene deprivatie (IAD). In onze studie werden groepen van patiënten geïdentificeerd die niet geschikt zijn voor intermitterende hormonale therapie, gebaseerd op enkele variabelen met predictieve waarde voor progressie. Door anderen werden overeenkomstige bevindingen gedaan en daarom is het aan te raden om intermitterende hormonale therapie te reserveren voor bij voorkeur patiënten met niet-gemetastaseerde ziekte met een licht tot matig verhoogd PSA en een relatief laag ziektevolume. Patiënten met een lokaal recidief of diegenen die niet sterk genoeg zijn voor curatieve therapie kunnen voordeel hebben van IAD, hoewel deze patiënten mogelijk jarenlang geen hormonale therapie nodig hebben zonder nadelige invloed op hun overleving. In één studie werd geen verschil gevonden in prostaatkanker-specifieke overleving bij patiënten, die niet sterk genoeg waren voor curatieve therapie, na randomisatie voor directe of uitgestelde ADT bij progressie [33]. In deze studie overleed 26% van de patiënten in de uitgestelde arm zonder ooit therapie te hebben gehad. Dit suggereert dat actief vervolgen een goede alternatieve behandeling voor ADT of zelfs voor IAD kan zijn, bij patiënten met laagvolume ziekte. Er is meer bewijs nodig voor deze situaties dat intermitterende hormonale therapie kan leiden tot een betere overleving, zeker omdat het de patiënt kan schaden door de bijwerkingen die optreden tijdens de behandeling. Een andere optie zou kunnen zijn om alleen een antiandrogeen te geven ter voorkoming van bijwerkingen van chemische castratie.

Patiënten met slechte prognostische kenmerken en hormonale therapie hebben mogelijk meer voordeel van een vroegtijdige omzetting naar alternatieve behandelingen en toekomstig onderzoek voor deze patiënten moet zich richten op de huidige nieuwe medicamenten. Uiteindelijk is de overleving het

belangrijkste eindpunt voor prostaatkankerbehandeling en alle andere eindpunten dienen als surrogaat. De follow-up duur in onze studie is kort en er is sprake van 'underpowering' zodat geen overlevingsverschil kon worden aangetoond en bovendien werd klinische progressie als surrogaat eindpunt gebruikt. Toekomstig onderzoek en lopende studies naar intermitterende therapie kunnen ons wellicht meer informatie verschaffen over de verschillen in overleving. Nieuwe fase III trials zijn feitelijk noodzakelijk ter bevestiging dat IAD de overleving van prostaatkanker niet in gevaar brengt. Wij hebben gevonden dat patiënten met een lage PSA nadir een significant hoger risico op progressie hebben met IAD dan met continue ADT. Dus bij deze groep lijkt het erop dat het achterhouden van ADT de patiënt kan schaden. Dit is een opmerkelijke uitkomst en tegenstrijdig met de bevindingen door anderen dat PSA nadir een sterke voorspellende factor is voor overleving [34]. Dit is voor zover bekend nooit eerder gerapporteerd en deze bevinding moet gevalideerd worden in nieuwe klinische trials.

In onze studie is er geen voordeel van kwaliteit van leven gebleken waarschijnlijk door een incompleet testosteronherstel in de tussenliggende periodes zonder hormonen ondanks een vermindering van de bijwerkingen. De verklaring hiervoor is onduidelijk en vraagt meer onderzoek. Men dient zich te realiseren dat studie-uitkomsten van kwaliteit van leven en bijwerkingen een bias bevatten omdat dubbelblinde placebo-gecontroleerde studies nooit zijn uitgevoerd. De wetenschap van de patiënt dat hij zich in de intermitterende arm bevindt kan invloed hebben op het bijwerkingen profiel. Een andere factor met invloed op de kwaliteit van leven meting is het langdurige castratieniveau na de LHRH agonist inductieperiode. Onderzoek in de toekomst moet zich daarom mede richten op intermitterende therapie met alleen een antiandrogeen. Data over de consequenties van IAD op lange termijn wat betreft de bijwerkingen zijn niet beschikbaar, maar worden wel verwacht in de nabije toekomst als van de lopende trials de eindresultaten beschikbaar komen.

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Chapter

11

Appendix

Abbreviations
Dankwoord
List of Publications
Curriculum Vitae

Abbreviations

ADT	androgen deprivation therapy
Ar	Argon gas
BDFS	biochemical disease-free survival
CAD	continuous androgen deprivation therapy
CRT	conformation radiotherapy
CT	computerized/computed tomography
DIL	dominant intraprostatic lesion
3D-CRT	threedimensional-conformation/conformed radiotherapy
EBRT	external beam radiotherapy
GI	gastrointestinal
GU	genitourinary
Gy	Gray
HIFU	high-intensity focused ultrasound
IAD	intermittent androgen deprivation therapy
IMRT	intensity-modulated radiotherapy
IQR	interquartile range
LHRH	luteinizing hormone-releasing hormone
LN	liquid nitrogen
LP	laparoscopic prostatectomy
LUTS	lower urinary tract symptoms
MAB	maximal androgen blockade
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NA	not available
NADT	neoadjuvant androgen deprivation therapy
NVB	neurovascular bundle
OP	open prostatectomy
PS	performance status
PSA	prostate specific antigen
PTV	planning target volume
QOL	quality of life
RALP	robot-assisted laparoscopic prostatectomy

RT	radiotherapy
SD	standard deviation
TRUS	transrectal ultrasound
TURP	transurethral resection prostate
UTI	urinary tract infection

Dankwoord

Op de dag van de promotie sta je er alleen voor, maar het onderzoek dat leidt tot het schrijven van een proefschrift komt niet in je eentje tot stand. Ik ben dan ook veel dank verschuldigd aan iedereen die heeft bijgedragen aan dit proefschrift. Zonder de goede ideeën die werden aangedragen en de logistieke ondersteuning zou het niets zijn geworden. Ook de toestemming van patiënten voor dataverzameling en hun enorme bereidheid om bij te dragen aan het onderzoek zijn onontbeerlijk geweest voor de verschillende studies. Zonder iemand te kort te willen doen, wil ik een aantal mensen persoonlijk bedanken.

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bestralingstechnieken waren voor mij als relatieve leek op dit gebied essentieel om de materie te begrijpen. Dank ook voor de beoordeling van andere delen van dit boekje. Veel succes met de verdediging van je eigen proefschrift.

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G.M. McColl, M.S., beste Gill. Vanaf het prille begin van het onderzoek naar goudmarkerimplantatie in de prostaat heb jij mij enorm ondersteund met de vragenlijsten, de follow-up en het doorspitten van patiëntendossiers. Je draagt veel bij aan onderzoek van anderen, maar ik hoop ooit toch ook een proefschrift van jou te kunnen lezen.

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D. Badhauser, M.S., dear Dirk. When I presented my research on the EAU in Milan 2008 you asked me to do join a research project on intermittent hormonal therapy with the aid of the TULP study data. I visited you and mr. Schaaf in Frankfurt and we exchanged the ideas for the study after some great pizza. We immediately started working on the subject, but it turned out to be quite a lot of work to get the job done. Finally, we succeeded to get the article being published and it has become an important part of this thesis. Thank you for the excellent cooperation. I wish you all the best in your new job and hope to meet again soon. Auf wiedersehen.

Dr. H. Vergunst, beste Henk. In mijn periode als AIOS urologie in het CWZ heb ik de start van cryochirurgie van de prostaat meegemaakt. Jij hebt deze therapie in Nederland nieuw leven ingeblazen en hoewel het niet gemakkelijk is als pionier te moeten beginnen, heb je getoond dit met toewijding te willen doen. Er is een fraai overzichtsartikel uit voortgekomen met medewerking van Eveline Broers, in een sterk tijdschrift. Ik hoop dat je blijft vernieuwen en het onderzoek op dit gebied continueert. Dank voor je enthousiasme en de gedachtenwisselingen die we gedurende mijn tijd in het CWZ hebben gehad.

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Leden van de manuscriptcommissie. Hooggeleerden Jelle Barentsz, Ad Hermus en Jeroen van Moorselaar zeer veel dank voor het beoordelen van het manuscript en de positieve woorden.

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List of Publications

Highly selective embolization of bilateral cavernous arteries for post-traumatic penile arterial priapism
JF Langenhuijsen, Y Reisman, JA Reekers, ThM de Reijke
Int J Impot Res 2001; 13: 354-6.

Results of ankle fractures with involvement of the posterior tibial margin
JF Langenhuijsen, MJ Heetveld, JM Ultee, EP Steller, RM Butzelaar
J Trauma 2002; 53: 55-60.

De rol van hormonale therapie bij uitwendige radiotherapie van prostaatcarcinoom
JF Langenhuijsen, PFA Mulders
Ned Tijdschrift voor Urologie 2005; 1: 16-22.

Cryochirurgie van de prostaat
RLFM Corten, H Vergunst, JF Langenhuijsen
Urologen Vademecum 2006; 1: 2-3.

Cryochirurgie van de prostaat
JF Langenhuijsen, H Vergunst, RLFM Corten
Kanker 2007; 31: 12-5.

Ultrasound-guided transrectal implantation of gold markers for prostate localization during external beam radiotherapy: complication rate and risk factors
JF Langenhuijsen, EN van Lin, LA Kiemeney, LP van der Vight, GM McColl, AG Visser, JA Witjes
Int J Radiat Oncol Biol Phys 2007; 69: 671-6.

Postoperatieve gastrointestinale dismotiliteit na cystectomie
AF van der Meer, JF Langenhuijsen, ACITL Tan, HFM Karthaus
Ned Tijdschrift voor Urologie 2007; 7: 188-91.

Cryosurgery for prostate cancer: an update on clinical results of modern cryotechnology
JF Langenhuijsen, EM Broers, H Vergunst
Eur Urol 2009; 55: 76-86.

Rebuttal from authors re: J. Stephen Jones. Ten misconceptions regarding cryotherapy for prostate cancer
H Vergunst, JF Langenhuijsen
Eur Urol 2009; 55: 55-8.

Hormonale voorbehandeling
JF Langenhuijsen, JA Witjes
Handboek Prostataandoeningen, hoofdredacteur prof. dr. T. Boon
(Uitgeverij De Tijdstroom, Utrecht, 2009).
Hoofdstuk 17.12: 425-8.

Intermitterende hormonale behandeling
JF Langenhuijsen, JA Witjes
Hoofdstuk 18.2: 493-5.

De eerste Nederlands ervaringen met cryochirurgie voor het prostaatcarcinoom
EMP Broers, JF Langenhuijsen, H Vergunst
Ned Tijdschrift voor Urologie 2010; 1: 19-23.

Hand-assisted retroperitoneoscopic versus standard laparoscopic donor nephrectomy: HARP trial
LF Dols, NF Kok, T Terkivatan, TC Tran, FC d'Ancona, JF Langenhuijsen, IR zur Borg, IP Alwayn, MP Hendriks, IM Dooper, W Weimar, JN IJzermans
BMC Surg 2010; 10: 11.

Neoadjuvant androgen deprivation for prostate volume reduction: the optimal duration in prostate cancer radiotherapy
JF Langenhuijsen, EN van Lin, AL Hoffmann, I Spitters-Post, JA Witjes, JH Kaanders, PF Mulders
Urol Oncol 2011; 29: 52-7.

Continuous vs. intermittent androgen deprivation therapy for metastatic prostate cancer
JF Langenhuijsen, D Badhauser, B Schaaf, LA Kiemeney , JA Witjes, PF Mulders
Urol Oncol 2011 May 9. [Epub ahead of print]

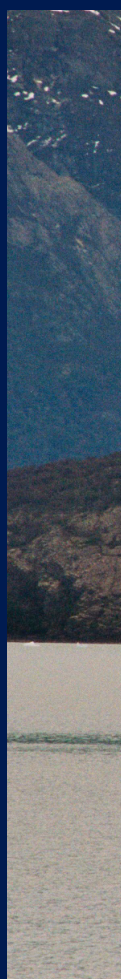
Reduction of treatment volume and radiation doses to surrounding tissues with intraprostatic gold markers in prostate cancer radiotherapy
JF Langenhuijsen, RJ Smeenk, RJ Louwe, P van Kollenburg, JH Kaanders, JA Witjes, EN van Lin
Clin Genitourin Cancer 2011; 9: 109-14.

Postprostatectomy ultrasound-guided transrectal implantation of gold markers for external beam radiotherapy: technique and complication rate
JF Langenhuijsen, R Donker, G McColl, LALM Kiemeney, JA Witjes, ENJTh van Lin
Submitted.

Laparoscopische en retroperitoneoscopische adrenalectomie: de resultaten bij 100 patiënten
JF Langenhuijsen, FCH d'Ancona
Accepted (Ned Tijdschrift voor Urologie).

Curriculum Vitae

Hans Langenhuijsen werd geboren op 27 oktober 1970 te Groningen. In 1974 verhuisde het gezin van Paterswolde naar Laren (NH). Hij zat in Hilversum op het Gemeentelijk Gymnasium en behaalde in 1989 het eindexamen. Het jaar na het eindexamen deed hij een deelcertificaat natuurkunde in Amsterdam en werkte aansluitend gedurende 7 maanden in Londen om in het nieuwe studiejaar te kunnen starten met Geneeskunde aan de Universiteit van Amsterdam. De interesse voor een snijdend specialisme werd tijdens de studie snel gewekt en daarom verrichtte hij wetenschappelijk onderzoek bij de afdeling vaatchirurgie van het AMC. Aan het einde van de basisopleiding koos hij voor een coschap traumatologie in Pretoria, Zuid-Afrika en een oudste coschap heelkunde in het Onze Lieve Vrouwe Gasthuis te Amsterdam. Na het behalen van het artsexamen in mei 1999 begon hij zijn medische loopbaan in de hoofdstad als AGNIO Chirurgie in het St. Lucas Andreas Ziekenhuis. Dat jaar ontwikkelde zich de wetenschappelijke interesse verder en werd de eerste publicatie geschreven. Er kwam een mogelijkheid voor een AGNIO plek urologie in het AMC bij prof. dr. K.H. Kurth. Datzelfde jaar was de centrale selectie voor een opleidingsplaats urologie en werd hij aangenomen in het cluster Nijmegen. Tijdens de vooropleiding heelkunde in het Rode Kruisziekenhuis te Beverwijk (opleider prof. dr. R.S. Breederveld), woonde hij in Amsterdam en trouwde in maart 2003 met Jik. In december verhuisden zij naar Nijmegen en begon hij de opleiding urologie in januari 2004 aan het UMC St. Radboud voor 2 jaar, onder leiding van prof. dr. J.A. Witjes. De ideeën voor het schrijven van dit proefschrift zijn toen ontstaan. De twee daarop volgende jaren werd het perifere deel van de opleiding genoten in het CWZ (opleider dr. H. Karthaus). In die periode werden de eerste twee kinderen in het gezin, Martje en Peer, geboren. Na het afronden van de opleiding urologie in december 2007 werd begonnen met een 1-jarig fellowship oncologie en laparoscopie op de afdeling urologie van het UMC St. Radboud onder leiding van prof. dr. J.A. Witjes. Een jaar later trad hij toe tot de medische staf op de pijler laparoscopie en endourologie met als specifieke aandachtsgebied minimaal invasieve operatietechnieken, zoals de laparoscopische donornefrectomie, retroperitoneoscopische adrenalectomie en orgaansparende operaties waaronder de robot-geassisteerde partiële nefrectomie. Tijdens het tweede jaar als staflid werd het derde kind, Taeke, geboren.



Advanced diagnostics for prostate cancer have enlarged the top of the iceberg, which may lead to more curative treatments and complications.